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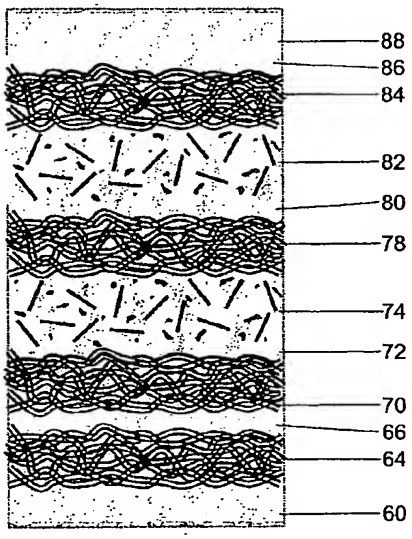

(57) Abstract: Flexible polymeric layered structures are disclosed. A first polymer layer (e.g. biocompatible polyurethane) is moulded over a support (e.g. a frame or another polymer layer) by drying from solution. A porous layer of polymer fibres (e.g. biocompatible polyurethane) is applied over the first polymer layer. A protective barrier layer (e.g. gold) is applied over the porous layer. A further polymer layer is applied over the porous layer, allowing attachment of the further polymer layer to the porous layer by keying. The polymer layers may be reinforced by fibres, e.g. carbon nanotubes. The layered structures are of particular use for heart valve leaflets.

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BIOCOMPATIBLE LAYERED STRUCTURES AND METHODS FOR THEIR MANUFACTURE

BACKGROUND

Field of the invention

The present invention relates to biocompatible layered polymeric structures and methods of forming such structures. Such structures are of use, for example, as biocompatible prostheses for implantation into the human or animal body. They may, for example, be of use in the cardiovascular system of the human or animal body.

The invention also relates to devices for implantation into the human or animal body and methods for forming such devices. Typical devices include prosthetic heart valves, but the invention is not necessarily limited to this.

Related art

There is significant interest in the use of structures formed of synthetic materials as implantable prostheses in the human or animal body. Prostheses of particular interest are prosthetic valves for use in replacing diseased or damaged valves in the heart.

Heart valve replacement devices have been in clinical use for over forty years with relatively acceptable results. There are shortcomings to the devices and further improvements are possible and desirable. There are generally two types of conventional heart valve replacement device - mechanical and biological.

Mechanical valves have rigid, biologically inert, synthetic components (e.g. metals or their alloys or pyrolytic carbon). There are a variety of designs such as caged-ball, tilting disc or tilting hemi-disc valves in which movement of the valve occluding component is restrained at a hinge, by a guide rail, or by a cage. Mechanical valves do not resemble natural valves and are associated with non-physiological flow patterns. Though they are durable within the body, they carry a risk of platelet aggregation or blood clot on or around the valve, which in turn risks spread of thrombus or platelet aggregates anywhere in the body (thrombo-embolism), necessitating life-long anticoagulant or anti-platelet drug therapy, with its attendant problems and risks.

Biological valves have components derived from biological sources (typically the aortic valve of the pig, or the pericardium of the calf), and mimic the natural aortic heart valve in appearance and in function (particularly

in flow pattern through the valve). They have a lower risk of thrombosis and thrombo-embolism than mechanical valves and may be used without anti-coagulants. However, they are vulnerable to wear and to degradation by the body, resulting in limitation of durability and the risk of further surgery for replacement of the device. The risk of degeneration is greater in young people than in the elderly, severely restricting the use of biological valves in the young, who are generally given mechanical valves (with their inherent life-long anti-coagulant and thrombo-embolic risk).

One approach to improving heart valve devices, in the hope of combining the lower thrombo-embolic and anti-coagulant risks of biological valves with improved durability over that seen in current biological valves, is the use of flexible polyurethanes to fabricate valve replacement devices that mimic natural heart valves in appearance and function (particularly in flow patterns through the valve). Heart valves constructed from certain polyurethanes, particularly those with proven inherent biostability, have been shown to function well in experimental studies, though ultimate durability and resistance to leaflet tearing remain sources of concern. Flexible synthetic valves have now been recognised (e.g. by the FDA) as a distinct group of replacement heart valve devices.

Explanations of the natural function and structure of cardiac valves (in particular of mitral valves) is given in WO 01/41679 and WO 03/037227. Those explanations are not repeated here, but the content of those two documents is incorporated herein by reference.

US-A-4,687,483 discloses a heart valve prosthesis having an annular support frame for supporting three flexible tissue valve components. It is suggested in that document that tissue formed of bovine pericardium or porcine aortic valves is particularly suitable for the flexible tissue valve components. It is also suggested that synthetic materials might be used, such as a polyurethane.

Polyurethanes have become the materials of choice for synthetic leaflet heart valves. Some polyurethanes are available that are resistant to degradation when implanted into the body. A preferred valve design has three valve leaflets attached to a support frame. WO 01/41679 describes a method of manufacturing a polyurethane valve leaflet on a moulding former. The material used is Elast-Eon ™ manufactured by Elastomedic of Sydney, Australia. The moulding former is dipped into a solution of the polyurethane and dried to leave a coating on the moulding former of about 0.1 mm thickness.

For a thicker leaflet, sequential multiple dips may be carried out.

D. J. Wheatley et al, "Polyurethane: material for the next generation of heart valve prostheses?", European Journal of Cardio-thoracic Surgery 17 (2000) pp. 440-448 discloses the results of research on prosthetic heart valves implanted in sheep. The study compared the behaviour of rigid mechanical valves with flexible polyurethane valves and porcine bioprosthetic valves. The polyurethane used was not biostable.

D. J. Wheatley et al ("Hydrodynamic function of a biostable polyurethane flexible heart valve after six months in sheep", The International Journal of Artificial Organs, Vol. 24, No. 2, 2001, pp. 95-101) discloses the results of further research on prosthetic heart valves implanted in sheep. A three leaflet valve design was used, having a polyetheretherketone (PEEK) frame and leaflets formed of biostable polyurethane. Two forms of polyurethane were used. Both were manufactured by CSIRO Molecular Science of Melbourne, Australia. These polyurethanes are based on a 4,4'-methylenediphenyl diisocyanate (MDI) hard segment with a polysiloxane soft segment. All of the formulations contained approximately 40% hard segment. One incorporated a diol chain extender (EV3.35) and the other a diamine chain extender (EV3.34).

Further details of these polyurethane materials are contained in WO 92/00338, WO 98/13405, WO 99/03863, WO 9950327, WO 00/64971, WO 01/07499 and P. A. Gunatillake et al ("Poly(dimethylsiloxane) / poly(hexamethylene oxide) mixed macrodiol based polyurethane elastomers. I. synthesis and properties", J. Appl. Polym. Sci. 2000; 76: pp. 2026-2040). A suitable silicon-based polycarbonate is described in WO 98/54242. The content of these documents is hereby incorporated by reference.

Cacciola G. et al ("A synthetic fiber-reinforced stentless heart valve", J. Biomech. 2000, 33(6), pp. 635-658) discloses a study of a fibre-reinforced valve design in which long fibres are laid down in a circular, sinusoidal or similar pattern around the leaflets, using a spinning process. The valve was synthesised from an ethylene-propylene rubber. The entire valve, including sinuses and a containing cylinder, was shaped as a single unit. The paper described laboratory tests and computer models, but presents no durability data nor any animal studies.

Daebritz S.H. et al ("Introduction of a flexible polymeric heart valve prosthesis with special design for aortic position", European Journal of Cardio-thoracic Surgery 2004, 25, pp. 946-952) disclose a synthetic

polymeric heart valve. The valve is a constructed entirely of various grades of a polycarbonateurethane material. The support frame (stent) is formed by dipping and contains an integral stiffening ring of titanium alloy. Softer leaflet material is added by what is described as "dropping" techniques. The leaflets are separated by laser trimming. The profile of the valve is high to minimise stress and strain peaks at the leaflet commissures. The opening is described as almost complete to the optimum circular orifice. The valve is described as having achieved 300 million cycles in fatigue testing. In animal trials, a valve tear was reported, which is a serious concern.

Mackay T.G. et al ("New polyurethane heart valve prosthesis: design, manufacture and evaluation", Biomaterials 1996; 17, pp. 1857-1863) and Mackay T.G. et al ("In vitro function and durability assessment of a polyurethane heart valve prosthesis", Artificial Organs 1996; 20, pp. 1017-1025) describe a heart valve leaflet design in which the leaflet geometry is elliptical in the radial direction and hyperbolic in the circumferential direction in the closed configuration for the valve. The leaflets were dip-coated from non-biostable polyurethane solutions onto relatively thick low-modulus polyurethane frames. This valve design attained durability in excess of 800 million cycles during in vitro fatigue testing, as

shown in Bernacca G.M. et al ("In vitro function and durability of a polyurethane heart valve: material considerations", J. Heart Valve Dis. 1996; 5, p. 538-542), Bernacca G.M. et al ("Polyurethane heart valves: fatigue failure, calcification and polyurethane structure", J. Biomed. Mater. Res. 1997; 34, p. 371-379) and Bernacca G.M. et al ("Polyurethane heart valve durability: effects of leaflet thickness", Int. J. Artif. Organs 1997; 20, p. 327-331). The design also provided suitable flow characteristics. However, the leaflet geometry, which provided for excellent sealing in the closed configuration, proved to be sub-optimal for small open orifice sizes, in part due to the bulk injection-moulded polyurethane frame.

A re-design of this valve geometry changed the hyperbolic angle from the leaflet free edge to the leaflet base. Furthermore, the low-modulus polyurethane frame was replaced with a high modulus PEEK frame, permitting the use of a thinner frame, thus increasing the valve orifice area. This improved the opening characteristics of the valve, but the geometry of the boundary region between the leaflet and the frame also prevented optimum washout of the inflow surface of the leaflets, resulting in some degree of thrombus deposition during animal implant experiments, as reported in Bernacca G.M. et al ("Durability and function of a polyurethane heart valve

after six months in vivo", Artificial Organs 1999; 23(7), p. 665) and D. J. Wheatley et al, "Polyurethane: material for the next generation of heart valve prostheses?", European Journal of Cardio-thoracic Surgery 17 (2000) pp. 440-448.

Some studies have suggested that the use of higher modulus synthetic elastomers for the leaflets is advantageous in terms of valve durability. However, this is at a potential cost to the haemodynamic function of the valve. Alternatively, it appears that reducing the thickness of the leaflets (in order to compensate for the stiffness of the material) might compromise the durability of the valve. This is disclosed in Bernacca G.M. et al ("Hydrodynamic function of polyurethane prosthetic heart valve: influences of Young's modulus and leaflet thickness", Biomaterials 2002; 23, pp. 45-50) and Bernacca G.M. et al ("Comparison of prosthetic valve hydrodynamic function: objective testing using statistical multilevel modelling", J. Heart Valve Dis. 2004; 13, pp. 467-477).

The nature of the materials used in existing bioprosthetic valves is that the development of a small tear can lead to rapid progression of the tear. This is of course undesirable in the clinical environment. It is preferred that any tear or other defect that arises

should progress only slowly, so that the failure can be detected to leave enough time for medical intervention.

Further details of heart valve designs are disclosed in Bernacca G.M. et al ("Surface modification of polyurethane heart valves: effects on fatigue life and calcification", Int. J. Artif. Organs 1998; 21, pp. 814-819) and Raco L. et al ("A study of HITS generation in a polyurethane heart valve: comparison with a mechanical valve and a bioprosthesis", Artificial Organs 1999; 23(7), pp. 668).

Computer-aided modelling of fluid-structure interactions are known. One effective known way to simulate the interaction of an elastic material with a viscous incompressible fluid is the immersed boundary (IB) method disclosed in Peskin C. ("The immersed boundary method", Acta Numerica, 2002, 11, pp. 1-39) and Peskin C.S. and McQueen D.M. ("A three dimensional computational method for blood flow in the heart 1. Immersed elastic fibres in a viscous incompressible fluid", Journal of Computational Physics, 1989, 81, pp. 372-405).

Adaptations of the IB code have been used to model chorded prosthetic mitral valve designs in Watton P.N. et al ("Modelling chorded prosthetic mitral valves using the immersed boundary method", Proceedings of the 26th

International Conference of the IEEE Engineering in Medicine and Biology Society, San Francisco, 2004, pp. 3745-3748).

Various publications describe prosthetic heart valve designs. Several of these disclose trileaflet heart valve designs in which a frame supports three flexible leaflets. See, for example, US-A-4,222,126, US-A-4,364,127, US-A-4,687,483, US-A-5,376,113, US-A-5,500,016, US-A-5,562,729, US-A-6,165,215, US-B-6,596,024, WO 98/32400, WO 01/41679, WO 02/100301, US 2003/114924, US-B-6,454,798, WO 00/21469, WO 02/074201, US 2003/078652, WO 01/05334, US 2003/069635 and WO 2004/082536.

In US 2003/183982, a method is described for manufacturing thin membranes for use as heart valve leaflets. A defined thickness distribution is achieved by applying several layers of a polymer solution.

Several documents focus of the design of the frame for the valve. See, for example, US-A-4,888,009, US-A-5,800,527 and US-A-6,086,612 (a mitral valve design).

Several documents describe the way in which a replacement heart valve should be attached to a sewing cuff for

suitable surgical implantation. See, for example, US 2003/109923 and US 2002/055773. Some disclose a valve design in which the implant has two separate parts. In a first part, a sewing cuff ring can be implanted first, and a second part, holding the valve leaflets, can be fixed to the sewing cuff ring. See, for example, US-A4,705,516, US-A-4,892,541, US-B-6,468,305 and US 2004/030381.

SUMMARY OF THE INVENTION

First development

A first development of the invention is described, in several aspects, along with preferred and/or optional features. A second development of the invention is described later, in several aspects, along with preferred and/or optional features. Features of the first or second developments (including preferred and/or optional features) may be combined in any combination, unless the context demands otherwise.

One of the techniques for manufacturing polymer heart valves is the dip moulding technique outlined above. With this technique valve leaflets are formed on a shaped mould which is dipped into a solution of polymer and then dried. This technique allows for a simple and practical

manufacturing method and has been used successfully to fabricate synthetic flexible leaflet heart valves. The present inventor has realised that there are a number of problems with the technique and in the materials used for valve fabrication which impose major constraints on the development of this type of valve for clinical use. In particular, it can be difficult to form a layer of flexible polymeric material on a support structure if the support structure is affected by (e.g. dissolves in) the solvent used in the polymer solution. Furthermore, it can be difficult reliably to obtain a leaflet having the desired thickness of suitable uniformity across the leaflet using multiple dips of the mould into the polymer solution. This is because the solvent tends to dissolve or otherwise degrade the already-formed and dried polymer on the mould.

In addressing this problem, the inventor has realised that the resultant first development of the invention has wider applicability than the field of heart valve prostheses. For example, the first development may also be used in other application where contact with blood is likely, such as in other cardiovascular devices (e.g. artificial blood-conducting tubes, lining of artificial left heart assist devices or pumps, patch material for use in blood-contacting situations, etc.).

In a general aspect of this first development, the present invention provides a protective barrier layer between a support of polymeric material and a layer of polymeric material in a flexible polymeric structure.

In a first preferred aspect of the first devlopment, the invention provides a method of manufacturing a flexible polymeric structure for a device for implantation into the human or animal body, the method including the steps:

(i) providing a support of polymeric material;

(ii) applying a protective barrier layer over the support;

(iii) applying a liquid layer including a solvent over the protective barrier layer; and

(iv) removing the solvent from the liquid layer to leave a layer of polymeric material over the protective barrier layer,

thereby sandwiching the protective barrier layer between the support and the layer of polymeric material.

The support may be another, first, layer of polymeric material (preferably flexible), the layer defined above being a second layer of polymeric material.

Alternatively, the support may be a more rigid support member on which the flexible layer of polymeric material is mounted. For example, in the case where the device is a prosthetic heart valve, the support may be a support

frame on which one or more flexible valve leaflets are mounted.

The invention allows the polymeric layer to be applied to the support without causing significant deterioration of the support. This is made possible by the use of the protective barrier layer, which can protect the support from being degraded or dissolved by the solvent.

Typically, the support is formed from a material that is affected by (e.g. dissolves in) the solvent used in the liquid layer. In the case where the support is a first polymeric layer, it may be formed by applying a liquid layer to a mould surface and subsequently removing solvent from said layer. The solvent can be removed by drying the layer at ambient temperature, under reduced pressure and/or at an elevated temperature, to reduce the time of removal of the solvent.

Preferably, the method includes the additional steps of:

(v) applying a further protective barrier layer over the layer of polymeric material;

(vi) applying a liquid layer including a solvent over said further protective barrier layer; and

(vii) removing the solvent from the liquid layer to leave a further layer of polymeric material over said further protective barrier layer.

In this way, it is possible for the support to be formed of a similar material to the layer(s) of polymeric material. This is advantageous because biological implant devices should be biostable, and only some materials have suitable combinations of biostability and mechanical properties to carry out the function required of the device. Thus, using the same or similar material for the support as for the layer(s) without degradation of the support allows a suitable device to be formed in a relatively simple manner.

The method may include further sequential steps of applying protective barrier layers and further layers of polymeric material in order to provide a layered flexible polymeric structure having a desired thickness. Preferably, the total mean thickness of the layers of polymeric material including the protective barrier layers is at least 50×10^{-6} m, more preferably at least 100×10^{-6} m. This thickness is preferably at most 1 mm, more preferably at most 500×10^{-6} m or even at most 250×10^{-6} m. In the case where the support is not a layer of polymeric material but is a support member such as a frame, these preferred values for thickness do not include the thickness of the support member. Typically, in the case of flexible structures such as valve leaflets, the thickness is not uniform across the

structure. For example, in a leaflet of total mean thickness of about 150 x 10^{-6} m, there may be portions of the leaflet of thickness as high as 400-500 x 10^{-6} m.

The inventor has realised that the production of a layered structure may provide advantages for the long-term use of the structure, e.g. at an implantation site in the body. Each layer may have only a small thickness, thereby avoiding the likelihood of a large defect affecting the performance of the structure. It is considered that the layered structure will limit the maximum size of possible defects (e.g. bubbles of gel particles) to the thickness of the layer in which they occur.

The method may include the step of applying an outer layer of polymeric material over the final protective barrier layer. This is because, as set out below, a polymer layer may be more firmly affixed at the outer surface of a device for implantation in the human or animal body than a typical protective barrier layer.

As set out above, the protective barrier layer or layers are of use in protecting the underlying material from solvent degradation during manufacture. Additionally, these layers may provide protection to the underlying material from environmental degradation. For example,

when the structure is implanted into the human or animal body, it may be exposed to enzymatic activity and/or biological attack. The sequential layers of the structure may provide a series of protective barriers against environmental degradation.

The material of the protective barrier layer is typically one that is inert to the solvent used in the liquid layer. The present inventor has found that noble metals (or other inert metals) are particularly suited to this application. Gold, for example, has been found to be suitable. Gold-palladium is also a suitable material. However, other materials may also be used. Typically, the material of the protective barrier layer is selected from gold, platinum, silver, palladium, nickel, copper, chromium or an alloy including at least one of these metals, or carbon.

The protective barrier layer is preferably thick enough to prevent significant deterioration of the first polymeric layer by the solvent yet thin enough not to have a detrimental effect on the flexibility of the layered flexible polymeric structure.

The barrier layer may be at least 1×10^{-9} m (i.e. 1 nm) thick, preferably at least 10×10^{-9} m and more preferably at least 35×10^{-9} m thick. The thickness required in

order to protect the underlying surface from attack by the solvent of the liquid layer depends on the surface roughness of the surface to be protected. In general, smoother surfaces require only a thin protective barrier. As will be discussed in more detail below, rougher surfaces (e.g. fibrous meshes) may require thicker protective barrier layers.

Preferably, the barrier layer does not have a significant influence on the mechanical properties of the flexible structure. Thus, the upper limit for the thickness of the protective barrier layer may be up to 500×10^{-9} m, more preferably up to 300×10^{-9} m.

The required thickness of the protective barrier layer will depend to some extent on the material of the barrier layer. The preferred figures given above may be applied to a gold-containing barrier layer, for example.

Carbon is of interest as the material of the protective barrier layer due to its inherent biocompatibility.

The protective barrier layer may be formed using a known technique for forming thin films. For example, sputter deposition may be used. Either DC sputtering or RF magnetron sputtering is appropriate, depending on the material to be deposited and the thickness required.

Evaporation deposition or laser ablation deposition may be used, again depending on the material to be deposited. In general, the technique used should allow a coating of substantially uniform thickness to be built up.

Preferably, the liquid used to form the polymeric layer is a solution of the polymer in the solvent. However, the liquid can be a suspension of the polymer in the solvent, or it can be a slurry. The term "solvent" is intended to define a liquid that would, unless prevented by the protective barrier layer, tend to dissolve or otherwise degrade the polymeric material of the first layer.

The use of dip-coating to form the layers of polymeric material is particularly preferred due to the ease with which layers may be formed of the required thickness. It is capable of forming complex shapes. Furthermore, it is useful for processing polyurethanes with urea functional groups that are not amendable to thermal processing. Such materials tend to have their melting temperature close to their degradation temperature.

Preferably, the polymeric material used for each polymeric layer is the same. Alternatively, different polymeric materials may be used for different layers. For example, outer layers of the device may be formed

from materials having high biostability. The polymeric material used for the support is preferably the same (at least in terms of composition) as is used for the polymeric layer. Suitable polymeric materials include polyurethane materials. This is set out in more detail below. Preferably, the polymeric material is a biostable polymeric material such as a biostable polyurethane.

The flexible structure is preferably resistant to tearing and/or cracking. This is important for ensuring long-term service after implantation. Preferred ranges for some mechanical properties of the flexible structure are set out in more detail below.

The method may include the further step of fixing the flexible layered structure to a frame. The frame may be formed of the same or a similar material to the flexible layered structure. However, preferably it is more rigid than the flexible layered structure, e.g. due to its dimensions relative to the flexible layered structure.

Preferably, the method includes the further step of applying a protective barrier layer to the frame. This may take place before the formation of the first layer of polymeric material, which may be formed over the protective barrier layer formed on the support frame.

In a second preferred aspect of this first development, the present invention provides a layered flexible polymeric structure having a support of polymeric material, a layer of polymeric material and a protective barrier layer sandwiched between the support and the layer of polymeric material.

The layered flexible polymeric structure may be obtained by or may be obtainable by the method of the first aspect of the first development.

Preferably, the structure includes a further protective barrier layer sandwiched between the polymeric layer and a second polymeric layer. More preferably, the structure includes a third and optionally further polymeric layers interleaved with protective barrier layers.

Preferably, the individual layers of polymeric material are at least 10 x 10^{-6} m thick. They may, for example, be up to 100 x 10^{-6} m thick. Typically, their thickness is in the range 20-30 x 10^{-6} m. There may be three, four, five, six or more individual layers of polymeric material, separated from the adjacent layer by a protective barrier layer.

In a third preferred aspect of the first development, the invention provides an implantable device incorporating a

layered flexible polymeric structure according to the second aspect.

The device may include a frame for supporting the layered flexible polymeric structure. The frame may be formed of the same or different polymeric material to the material of the first and/or second polymeric layers.

Preferably, the device is a cardiovascular prosthesis for implantation into the human or animal body. More preferably, the device is a heart valve prosthesis. The device may be, for example, an aortic valve prosthesis or a mitral valve prosthesis. Alternatively, the device may be a flexible chamber, e.g. a flexible pumping chamber for use in a heart assist device.

The present inventor has realised that some polymeric materials of use in flexible structures for implantable devices tend to tear or crack under repeated flexural stress.

Accordingly, in a fourth aspect, the present invention provides a flexible polymeric structure for a device for implantation into the human or animal body, the structure having a polymeric matrix component formed of a polymeric material with a Young's modulus of at most 100 MPa and having disposed within it an arrangement of fibres formed

of a material with a Young's modulus of at least 500 MPa in the elongate direction of the fibres, said arrangement of fibres providing the structure with increased resistance to crack or tear propagation on repeated flexing of the structure in comparison to the material of the matrix component alone.

Preferably, the matrix material has a relatively low Young's modulus. This allows the material to be resiliently deformed easily (e.g. flexed). For example, the Young's modulus may be at most 30 MPa or, more preferably, at most 15 MPa. A typical lower limit for the Young's modulus of the matrix material is at least 5 MPa.

Preferably, the matrix material is relatively soft. It may have a Shore A hardness of at most 95, more preferably at most 90 or 88. The Shore A hardness may be at least 75, more preferably at least 80.

Preferably, the matrix material is synthetic. Typically, the material is organic non-vinyl polymer, inorganic non-vinyl polymer or vinyl polymer, or a blend or copolymer thereof.

In the case where the matrix material comprises organic non-vinyl polymer, the organic non-vinyl polymer may be

selected from polyethers, poly(ethylene oxide), polysulfides, poly(alkylene polysulfide)s, polyesters, PET, polycarbonates, polyamides, polyurethanes, polyhydrazides, polyimides, resoles, novolacs, urea-formaldehyde polymers and melamine-formaldehyde polymers.

In the case where the matrix material comprises inorganic non-vinyl polymer, the inorganic non-vinyl polymer may be a polysiloxane.

In the case where the matrix material comprises vinyl polymer, the vinyl polymer may be selected from polyethylene, polypropylene, polyisobutylene, PVC, PTFE, polystyrene, poly(acrylic acid), poly(α-methylstyrene), poly(1-pentene), polyacrylonitrile, polyacrylates, poly(methyl methacrylate), poly(vinyl acetate).

Typically, the matrix material comprises a polyurethane. Most preferably, the matrix material is a biostable polyurethane elastomer such as is described in WO 98/13405, WO 99/03863 or WO 00/64971, the contents of which published documents are incorporated herein by reference.

Of particular interest is a polyurethane elastomeric composition comprising a polysiloxane macrodiol according to Formula (I) on page 7 of WO 98/13405 and a polyether

macrodiol according to Formula (II) on page 10 of the same document and/or a copoly(ether carbonate) macrodiol according to Formula (III) on page 12 of the same document.

Also of interest is a polyurethane elastomeric composition comprising a chain extender including a silicon-containing diol of Formula (I) on page 4 of WO 99/03863. Optionally, the composition may include a soft segment macrodiol derived from a polysiloxane macrodiol and a polyether macrodiol. The polyether macrodiol may be according to Formula (II) on page 11 of the same document.

Also of interest is a siloxane-containing polyurethane-urea elastomeric composition derived from a silicon-containing diamine of Formula (I) on page 3 of WO 00/64971. Optionally, the composition may include a soft segment macrodiol derived from a hydroxy terminated polysiloxane macrodiol represented by Formula (II) on page 8 of the same document. Optionally, the composition may include a soft segment macrodiol derived from a polyether macrodiol according to Formula (III) on page 9 of the same document. A suitable copolymer for use in the composition is a copoly(ether carbonate) macrodiol represented by Formula (IV) on page 10 of the same document.

Preferably, the fibre material is a high strength material such as carbon fibre. The carbon fibres may be, for example, carbon nanotubes.

The individual fibres in the structure may have a high aspect ratio, e.g. 100:1 or higher. Preferably, the average width of the fibres is less than 5×10^{-6} m, more preferably less than 2×10^{-6} m. In the case of nanotubes, the average width may be significantly less than this, for example less than 5×10^{-9} m. The average length of the fibres is typically $1\text{-}1000 \times 10^{-6}$ m, more preferably at least 20×10^{-6} m and at most 200×10^{-6} m.

The Young's modulus of the reinforcing fibres may be significantly higher than the value of 500 MPa suggested above. For example, the Young's modulus may be at least 1 GPa, preferably at least 10 GPa, more preferably at least 50 GPa. For vapour grown carbon fibres, for example, the Young's modulus may be 100-300 GPa. For carbon nanotubes, the Young's modulus may be 500 GPa or higher, e.g. 1 TPa or above.

In any of the first, second or third aspects of this first development, set out above, preferred or optional features of the polymeric material may be the same as the

features set out above with respect to the matrix material of the fourth aspect.

Furthermore, the combination of the matrix material component and the arrangement of fibres of the fourth aspect may be used as the layer or layers of flexible polymeric material of any of the first, second or third aspects. This constitutes a fifth aspect of the first development of the invention. In this way, a layered flexible polymeric structure may be provided having high resistance to crack or tear propagation.

In a sixth aspect of the first embodiment of the invention, there is provided a method of manufacture of a flexible polymeric structure according to the fourth or fifth aspect, the method including the steps of:

forming a layer from a liquid containing the polymeric matrix component, or a precursor thereof, and the fibres; and

removing the liquid.

Preferably, the liquid is a mixture of the fibres and the polymeric matrix component, or a precursor thereof. The liquid is preferably prepared by electrostatic spinning. In such a process, a charge applied to the liquid during electrostatic spinning serves to disperse the fibres within the liquid. The resultant product of the

electrostatic spinning process is still a liquid due to starting liquid (solvent plus polymer) being sufficiently dilute. The liquid prepared in this way has been found to be particularly suitable for the formation of the layer of flexible polymeric material. Suitable voltages applied during the electrostatic spinning process are 5 kV or more, preferably 10 kV or more, more preferably 15 kV or more or even 20 kV or more. A suitable value has been found to be about 24 kV.

Preferably, the fibres chemically interact (e.g. bond) with the polymeric matrix component, or precursor thereof. The interaction may be via covalent bonding, hydrogen bonding, van der Waal's forces or ionic attraction.

Preferably, the fibres are carbon nanotubes. The carbon nanotubes may have been functionalised with at least one additional chemical species, for interaction with the polymeric matrix component, or precursor thereof. Preferably, the functionalised carbon nanotubes are biocompatible. Suitable functionalising groups for carbon nanotubes are NH_2 groups and/or COOH groups, for example.

Preferably, prior to the electrostatic spinning, the liquid is agitated to disperse the fibres through the

liquid. This agitation may, for example, be via ultrasonic or mechanical agitation.

Preferably, after preparation of the liquid by electrostatic spinning, the layer is formed by coating the liquid onto a mould or support. This layer formation may be according to any one of the other aspects of the invention described herein. In particular, the layer may be formed as one layer in a biocompatible layered structure according to other aspects of the invention described herein.

The present inventor has also realised that firm bonding between interfaces in a flexible polymeric structure formed using multiple steps is important to ensure integrity of the structure in use, particularly in use as an implanted device in the human or animal body.

Accordingly, in a seventh aspect of this first development, the present invention provides a device for implantation into the human or animal body having:

a support;

a porous layer on a surface of the support to form a keying interface on the surface;

a protective barrier layer formed over the porous layer; and

a layer of flexible polymeric material applied over the protective barrier layer,

wherein an interface part of the layer of flexible polymeric material is interlocked with the porous layer.

The inventor has found that this arrangement can provide a durable bond between the support and the layer of polymeric material.

In an eighth aspect of this first development, the invention provides a method of manufacture of a device for implantation into the human or animal body, including the steps:

(i) providing a support of polymeric material;

(ii) applying a porous layer on a surface of the support to form a keying interface on the surface;

(iii) applying a protective barrier layer over the porous layer;

(iv) applying a liquid layer including a solvent over the protective barrier layer; and

(v) removing the solvent from the liquid layer to leave a layer of polymeric material over the protective barrier layer,

whereby an interface part of the layer of flexible polymeric material is interlocked with the porous layer.

The following preferred or optional features may be applied to the seventh and/or eighth aspect of the first development. As will be clear, any of these features may also be combined, in any suitable combination, with any of the previously described aspects of the first development of the invention and/or preferred or optional features thereof, and/or with any aspects (including preferred or optional features) of the second development of the invention.

Preferably, the porous layer comprises a mesh of fibres.

Preferably, the interface part of the layer of flexible polymeric material includes elements of flexible polymeric material that are trapped in interstices in the porous layer. Typically, said elements are integral with the layer of flexible polymeric material. In this way, the layer of polymeric material may be provided with many anchors in the porous layer that serve to hold the layer of polymeric material with respect to the porous layer.

The component may include a further porous layer bonded to a surface of the layer of flexible polymeric material. In that case, said further porous layer may have a further protective barrier layer. There may be a further layer of flexible polymeric material applied over said further protective barrier layer so that an interface

part of said further layer of flexible polymeric material is interlocked with the further porous layer.

The flexible polymeric structure may be a laminate of a plurality of alternate layers of porous layer, protective barrier layer and flexible polymer layer, wherein an interface part of each flexible polymer layer is interlocked with its respective porous layer. For example, there may be three or more laminates in said structure.

The support may itself be a layer of flexible polymeric material. In that case, the structure preferably takes the form of a sheet. Preferably, however, the support is a relatively rigid member to which said layer of flexible polymeric material or laminate is attached. The support may, for example, be a frame.

Preferably, the layer of polymeric material is formed of the same material as set out with respect to any of the other aspects of the invention. It may include an arrangement of reinforcing fibres, as set out with respect to the fourth aspect of the first development.

Preferably, the protective barrier layer is formed of the same material as set out with respect to any of the other

aspect of the first development, e.g. the first aspect of the first development.

Preferably, as already mentioned, the porous layer is a fibrous mesh. The porous layer is typically formed of polymeric material. For example, any of the polymeric materials set out with respect to any of the other aspects of the invention may be used. However, where the porous layer is a mesh of fibres, typically the fibres have different mechanical properties to the bulk materials set out above.

Typically, there is no protective barrier layer formed between the surface of the support and the porous layer. This is to allow a firm bond to form between the support and the porous layer, because the strength and durability of this bond will affect the strength and durability of the structure as a whole.

The method of deposition of the porous layer onto the support preferably provides a mechanism for the bonding of the porous layer to the support. In the case where the material of the support is soluble in the same solvent as the material of the porous layer, the porous layer may be deposited from a solution of the material of the porous layer in a solvent. For example, the porous layer may be formed by rapid drying of the solvent during

transit of the solution so that the material applied to the surface of the support has only a small amount of solvent present. The material applied to the surface of the support may be viscous due to the small amount of solvent retained in the material. This small amount of solvent, before being removed from the layer (e.g. by drying) may serve to bond the material of the support to the material of the porous layer by dissolving a small amount of the material of the support before being removed.

In the case where the porous layer is a mesh of fibres, the mesh may be formed, for example, by electrostatic spinning (ESS). This is a known technique. Preferably, the technique used is substantially as set out in US 2004/0019374 (Hojeibane et al), the contents of which document is incorporated herein by reference.

Preferably, the composition of the porous layer is substantially the same as that of the support and/or the flexible polymer layer. However, as mentioned above, the porous layer may have different mechanical properties to the support and/or flexible polymer layer. In the case where the porous layer is a fibre mesh, the fibres may have higher Young's modulus and/or higher UTS than the material of the support and/or flexible polymer layer.

This is due to the molecular alignment that tends to occur during fibre formation.

Alternatively, the composition of the porous layer is different to that of the support and/or the flexible polymer layer. The composition may be selected, for example, to provide a porous layer having higher Young's modulus and/or higher UTS.

Preferably, the (or each) porous layer is at least 5×10^{-6} m thick, more preferably at least 10×10^{-6} m thick. The porous layer may be at most 40×10^{-6} m, more preferably at most 20×10^{-6} m thick.

A fibre mesh as set out above may also provide increased resistance to crack or tear propagation.

Second development

The inventor has also realised that some flexible devices for implantation into the human or animal body should have a high resistance to crack or tear formation or propagation but should also be highly flexible. For a typical material, increasing the thickness of the flexural part of such a device increases the crack or tear propagation resistance but also increases the force required to flex that part of the device.

Accordingly, in a first aspect of this second development, the present invention provides a device for implantation into the human or animal body having a layered flexible polymeric structure with a plurality of layers of flexible polymeric material, wherein:

for a first shape of the structure, at least part of a first one of said plurality of layers is in its minimum stress configuration; and

for a second, different, shape of the structure, at least part of a second one of said plurality of layers is in its minimum stress configuration,

so that said first and second layers urge the structure towards said first shape and said second shapes, respectively.

In this way, the device can be formed with a suitable thickness of flexible polymer layers so that it has improved resistance to crack or tear propagation but is also more easily flexed between the first and second shapes due to the urging of the first and second layers towards those shapes, respectively.

Preferably, the structure may be configured from the first shape to the second shape by bending or distension of at least part of the structure.

Preferably, the device has third and, optionally, further and subsequent, layers that are formed with different preferred shapes.

Preferably, the device is a cardiovascular prosthesis such as a heart valve. Preferably, the layered flexible polymeric structure forms a whole or part of a heart valve leaflet. A leaflet formed with this structure may therefore have different shapes in which at least one of the layers is minimally stressed. Thus, deformation of the leaflet may be bistable or multistable. This can assist in providing a heart valve leaflet that is thick enough to resist tearing and/or cracking but which is flexible enough to function satisfactorily.

In a second aspect of the second development, the invention provides a method of forming a device according to the first aspect of the second development, including the steps of:

forming a first layer of flexible polymeric material in a first shape;

deforming said first layer; and

forming a second layer of flexible polymeric material over the deformed first layer,

so that the first and second layers of flexible polymeric material have different preferred shapes.

Preferably, the layers of polymeric material are formed by drying a layer of a solution of the polymeric material in a solvent, as set out above with respect to the first development.

The method may include the step of applying a protective barrier layer over the first layer of polymeric material. This may serve to protect the first layer from dissolving in the solvent when the second layer of polymeric material is being formed. The application of the protective barrier layer and the protective barrier layer itself may be as set out with respect to the other aspects of the invention, above.

The material of the flexible polymeric layer may be as set out with respect to the first development of the invention, above.

Preferably, the first layer is formed on a mould having said first shape. Subsequently, the first layer may be deformed using a mould having a different shape. Alternatively, the first layer may be deformed by deforming the shape of the mould.

In a preferred embodiment, the invention provides a device for implantation into the human or animal body, the device having:

a support;

a porous layer on a surface of the support to form a keying interface on the surface;

a protective barrier layer formed over the porous layer;

a layer of flexible material applied over the protective barrier layer; and

at least one further layer of flexible material,

wherein an interface part of the layer of flexible material is interlocked with the porous layer,

the layer of flexible material having a polymeric matrix component formed of a polymeric material with a Young's modulus of at most 100 MPa and having disposed within it an arrangement of fibres formed of a material with a Young's modulus of at least 500 MPa in the elongate direction of the fibres, said arrangement of fibres providing the structure with increased resistance to crack or tear propagation on repeated flexing of the structure in comparison to the material of the matrix component alone, wherein:

for a first shape of the structure, at least part of a first one of said plurality of layers is in its minimum stress configuration; and

for a second, different, shape of the structure, at least part of a second one of said plurality of layers is in its minimum stress configuration,

so that said first and second layers urge the structure towards said first shape and said second shapes, respectively.

In a third aspect of the second development, the invention provides a synthetic replacement heart valve having at least two leaflets, the leaflets being movable from a natural configuration to open and closed configurations for the valve, the natural configuration being intermediate the open and closed configurations, the valve being in the natural configuration when at rest (e.g. prior to implantation), the valve further having an average blood flow direction, defining upstream and downstream directions for the valve,
wherein, in the natural configuration, at least one upstream bulge portion of at least one of the leaflets is more opened, compared to the closed configuration, than a corresponding downstream portion of the same leaflet, thereby facilitating opening of the valve from the natural configuration.

Preferably, each leaflet has a free edge at its downstream extremity. Each end of the free edges may be supported so that, in the closed configuration, the free edges of the leaflets meet substantially to seal the valve against reverse flow.

Preferably, each leaflet is supported at its lateral sides by a frame. Typically, said upstream bulge portion of said at least one leaflet is a lateral portion of said leaflet, adjacent the frame.

Preferably, an upstream concave portion of the leaflet, laterally adjacent said upstream bulge portion, is less opened than the bulge portion.

Preferably, each of the leaflets has an upstream bulge portion. Additionally or alternatively, each of the leaflets may have an upstream concave portion, e.g. disposed laterally between upstream bulge portions.

Most preferably, the valve has three leaflets. For example, the valve may be an aortic valve. The sub-commissural areas of the valve may correspond to the upstream bulge portions.

Typically, the bulge portions are arranged so that, in use in a pulsatile fluid flow, in one part of the pulsatile cycle, said bulge portions fill before said concave portions to promote opening of the leaflets and washout of the valve.

Preferably, the leaflets are attached over an outer surface of the frame, the inner surface of the frame

having a bevel meeting the leaflets, thereby providing a smooth fluid flow surface along the inner surface of the valve.

Alternatively, the outer surface of the frame may have a bevel at the free edge of the frame, over which bevel the leaflets bend when moving from the open configuration to the closed configuration. This bevel can therefore provide a support surface for the leaflet, avoiding sharp bending of the leaflet. Most preferably, the bevelled surface is a curved bevel. This can provide a smooth surface over which the leaflets can bend into the closed configuration, thereby further reducing any stress concentrations in the leaflet.

In a fourth aspect of the second development, the invention provides a method of manufacturing a synthetic replacement heart valve having at least two valve leaflets, the leaflets being movable from a natural configuration to open and closed configurations for the valve, the natural configuration being intermediate the open and closed configurations, the valve being in the natural configuration when at rest, the valve having an average blood flow direction, defining upstream and downstream directions for the valve,
the method including the step of forming the valve leaflets in the natural configuration, in which at least

one upstream bulge portion of at least one of the leaflets is more opened, compared to the closed configuration, than a corresponding downstream portion of the same leaflet, thereby facilitating opening of the valve from the natural configuration.

Preferred and/or optional features described with respect to the other aspects of the second development (particularly the third aspect, above) may be applied to this fourth aspect.

In a fifth aspect of the second development, the invention provides a method of manufacturing a device for implantation into the human or animal body, including manufacturing a flexible laminate of a support layer and a porous layer by the steps:

providing a support layer of polymeric material having an outer surface with a natural configuration;

distending the support layer to provide the outer surface with a distended configuration;

applying a porous layer to the outer surface; and

relaxing the laminate back towards the natural configuration.

Preferably, the distended configuration is a smoothly curved configuration, expanded from the natural

configuration. This allows the application of the porous layer to the outer surface in a uniform manner. This is particularly the case where the porous layer is applied via electrostatic spinning, as described with respect to the first development.

Alternatively, the distended configuration may be contracted from the natural configuration, to be less smoothly curved than the natural configuration. The advantage of distending the shape in this way is that the porous layer may be applied preferentially to some parts of the outer surface. Again, if the porous layer is applied via electrostatic spinning, as described with respect to the first development, the porous layer may preferentially be deposited at ridges and peaks in the outer surface.

Preferably, the natural configuration of the flexible laminate is a domed shape.

Preferably, the porous layer is a polymeric fibre mesh formed by electrostatic spinning.

Preferably, a protective barrier layer is applied to the porous layer. Preferably, a further layer of flexible polymeric material is applied over the protective barrier layer.

The method may include one or more of the further steps:

(i) distending said laminate of the support layer, porous layer, optional protective barrier layer and further layer of flexible polymeric material to provide a further outer surface with a distended configuration;

(ii) applying a further porous layer to the further outer surface;

(iii) relaxing the laminate back towards the natural configuration; and,

optionally, repeating steps (i) to (iii).

In this way, the structure may be built up in layers as required.

Preferably, the support layer or laminate provides a sealable enclosure. In this way, the support layer may be distended by inflation or deflation with a fluid.

Preferably, the device is a valve having two or more leaflets, the leaflets being formed by cutting the laminate to form free edges for the leaflets. Advantageously, the cutting of the laminate may provide a surplus sample of the laminate, said surplus sample being usable for quality control of the device.

Typically, where the device is a valve, the lateral sides of the downstream ends of the valve leaflets meet at commissural areas, said commissural areas forming ridged regions for concentration of the formation of the porous layer in the contracted configuration.

Preferably, the device is formed from a frame and at least two flexible leaflets moulded over the frame, the method further including the steps of moulding the support layer of polymeric material on a mould, the mould having a frame portion for location of the frame and leaflet moulding surfaces for moulding the leaflet shape, wherein the leaflet moulding surfaces are disposed on at least one separable part of the mould, separable from the frame portion to allow the moulded valve to be removed from the mould.

Preferably, in the mould, the frame portion in combination with the separable portion defines a recess for accommodating the frame thickness, so that the leaflets smoothly overlie the frame.

Preferably, the mould has one separable part per leaflet (e.g. three). This allows the leaflet moulding to be achieved and then the mould can be separated into parts, to allow each removal of the moulded valve components from the mould.

The method may further include the step of infusing fluid between the valve leaflets and the mould surface to separate the leaflets from mould. This provides a gentle way to remove the leaflets from the valve.

In a preferred embodiment, the invention provides a device for implantation into the human or animal body, the device having:

a support;

a porous layer on a surface of the support to form a keying interface on the surface;

a protective barrier layer formed over the porous layer;

a layer of flexible material applied over the protective barrier layer; and

at least one further layer of flexible material,

wherein an interface part of the layer of flexible material is interlocked with the porous layer,

the layer of flexible material having a polymeric matrix component formed of a polymeric material with a Young's modulus of at most 100 MPa and having disposed within it an arrangement of fibres formed of a material with a Young's modulus of at least 500 MPa in the elongate direction of the fibres, said arrangement of fibres providing the structure with increased resistance to crack or tear propagation on repeated flexing of the

structure in comparison to the material of the matrix component alone, wherein:

for a first shape of the structure, at least part of a first one of said plurality of layers is in its minimum stress configuration; and

for a second, different, shape of the structure, at least part of a second one of said plurality of layers is in its minimum stress configuration,

so that said first and second layers urge the structure towards said first shape and said second shapes, respectively.

Any of the preferred/optional features set out with respect to any of the aspects of either of the developments of the invention may be combined with this preferred embodiment of the invention.

In a further aspect, the invention provides use of a device according to the any of the above aspects of the invention in the manufacture of a prosthesis for implantation into the human or animal body for the treatment of a cardiovascular condition.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1-4 show progressive schematic steps in the formation of a synthetic flexible leaflet heart valve using a dip coating procedure.

Fig. 5 shows an optical transmission micrograph of a polyurethane sheet without reinforcing fibres with a cut artificially introduced.

Fig. 6 shows the polyurethane sheet of Fig. 5 after cyclical loading.

Fig. 7 shows an optical transmission micrograph of a polyurethane sheet with reinforcing fibres with a cut artificially introduced.

Fig. 8 shows the polyurethane sheet of Fig. 7 after cyclical loading.

Fig. 9 shows an SEM micrograph of an ESS polyurethane mesh spun onto a glass slide.

Fig. 10 shows an optical transmission micrograph of a construct formed of a polyurethane support layer, spun polyurethane mesh, protective barrier layer and overlying polyurethane layer.

Figs. 11-23 show schematic cross-sectional views of the progressive build-up of layers in a flexible laminated construct according to an embodiment of the invention.

Figs. 24-33 show SEM micrographs and X-ray elemental maps of cross-sections of constructs formed according to embodiments of the invention.

Figs. 34-39 illustrate different stages in the production of a synthetic flexible leaflet heart valve.

Figs. 40-42 show views from above of a partially-formed synthetic heart valve in different configurations.

Fig. 43 shows an exploded view of a combination of a frame and mould for forming a heart valve according to an embodiment of the present invention.

Fig. 44 shows a combination of a frame and mould for forming a heart valve according to another embodiment of the present invention.

Fig. 45 shows an exploded view of a multi-part mould and frame for forming a heart valve according to another embodiment of the present invention.

Fig. 46 shows a view of a frame separated from a sewing cuff support portion, for use with an embodiment of the present invention.

Fig. 47 shows a perspective view of a valve frame for use with an embodiment of the present invention.

Fig. 48 shows a sectional view of the valve frame of Fig. 47.

Figs. 49A-E illustrates a numerical model of a heart valve being sequentially opened due to a modelled pulsatile blood flow.

Fig. 50 shows a schematic process for designing a partially-open shape for a heart valve according to an embodiment of the present invention.

Fig. 51 shows an alternative partially-open shape for a heart valve according to an embodiment of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In what follows, the formation of a product using protective barrier layers will be described after first setting out a suitable method for forming a flexible polymeric layer on a support. Then the use of reinforcing fibres in a flexible polymeric structure will be described. Then the use of a porous layer to provide a keying interface between a support and a layer of flexible polymeric material will be described. Then a method for forming a layered device having more than one preferred shape will be described. These examples of the invention will be described with reference, where applicable, to a synthetic prosthetic heart valve. It is to be understood that at least some aspects of the invention are not necessarily limited to such a device and may have wider applicability.

After the descriptions of the formation of suitable flexible polymeric layered structures, preferred embodiments of the specific devices incorporating such materials will be described. The mode of formation of a synthetic flexible leaflet heart valve will be described, followed by a description of the particular preferred natural configuration for such a synthetic heart valve.

Fig. 1 shows a mould 10 for forming a synthetic replacement three-leaflet heart valve. The mould is formed from acetyl copolymer. In an alternative embodiment, the mould 10 is formed from stainless steel or other suitable material. The mould has the overall shape of a scalloped circular cylinder with three substantially ellipsoidal recesses 12, 14 formed in the side. The recesses cause the cross-sectional area of the mould to decrease from that of the substantially circular base to the top of the mould, at which top the recesses form a sharp three-way ridge. The side surface of the mould that is not recessed thereby has three upstanding peaks 16, 18 (the third peak is not shown in this drawing) disposed around the side surface of the mould, said peaks being coincident with the three-way ridge.

A valve frame 20 is shown in Fig. 2. The valve frame has an overall open cylindrical shape but with three substantially elliptical recesses formed downwardly from the top of the frame, forming frame peaks 22, 24, 26 that are upstanding from the base 28 of the frame. The frame is formed of PEEK having a flex modulus of about 4 GPa, an elastic modulus of about 3 GPa and T_g of 143°C.

In another preferred embodiment, the frame is formed from high modulus polyurethane having a Shore D hardness of 80-90D. In that case, the surface of the frame is

treated according to the invention as will be described in further detail below.

In a still further embodiment, the frame is formed of Delrin™. The material of the frame typically has a Shore hardness in the range 75-85D, with Young's modulus of 500 MPa to 3 GPa.

In order to form valve leaflets on the valve frame, the valve frame 20 is fitted over the mould 10 so that the peaks of the valve frame are in coincidence with the peaks of the mould. In this way, the recesses of the valve frame are also in coincidence with the recesses of the mould.

Next, the mould is attached to a handle, if required, and the mould carrying the valve frame is dipped into a polyurethane solution 30, as illustrated schematically in Fig. 3. Specific suitable polymers have already been mentioned. Of most use are polyetherurethane, polyetherurethane urea, polycarbonaturethane, or any of these formulated with a silicone co-soft segment or with surface modifying end groups such as silicone, fluorocarbon, polyethylene oxide, sulphonate, hydrocarbons or mixtures of these. A biostable formulation is preferred. Specifically, the material PurSpan™ is used. This material is available from The

Polymer Technology Group, of Berkeley, California 94710, USA. This material has an aromatic urea hard segment, a polyether soft segment and a silicone co-soft segment. The Shore hardness of the polymer is 80-85A. The Young's modulus is 10-20 MPa. The solvent used is dimethyl formamide but dimethyl acetamide or tetrahydrofuran may also be used.

The excess polyurethane solution is allowed to run off the dipped frame, leaving a thin, even coating of polyurethane solution on the frame and on the recessed surfaces of the mould. The frame is not degraded by the polyurethane solution. This is either because it is formed of a material (e.g. PEEK) that is inert to the solvent used in the polyurethane solution or because it has a surface treatment (as will be described below) that renders it inert to the solvent.

The coated frame and mould are dried in an oven at a suitable temperature. After the solvent has been removed in this way, the frame and mould combination is covered with a thin, flexible even layer of polyurethane.

After this drying step, the frame is removed from the mould. The flexible polyurethane layer remains attached to the frame but is detached from the mould. The frame and the flexible polyurethane layer is then attached

using known methods to a sewing ring, to give a synthetic replacement heart valve device 40 as shown in Fig. 4. Between the peaks 22, 24, 26 of the valve frame, the layer of flexible polymer retains the shape of the recessed surface of the mould. Thus, three flexible valve leaflets 42, 44, 46 are formed, their top edges meeting at a three-way ridge. The valve leaflets are, in fact, formed in one piece, with the parts of the polymer layer between the valve leaflets being attached to the peaks 22, 24, 26 of the valve frame. It will be understood that the valve leaflets will resist flow through the valve that forces their top edges together and will allow flow that forces their top edges apart.

Sewing ring 48 is attached to the bottom end of the valve frame in a known manner. Note that the drawing of Fig. 3 shows the valve from above in a foreshortened manner. Suitable dimensions for the valve will be apparent to the skilled person.

Further details on the specific construction steps in the formation of a flexible heart valve are set out below.

In one embodiment of the invention, a flexible polyurethane layer is applied to a support, also formed of polyurethane. The support may be another layer of polyurethane or it may be a mesh of polyurethane fibres

(as described below) or a relatively rigid support member such as a frame. In each case, the dip-coating method set out above for forming the flexible polymer layer has the disadvantage that the solvent used to form the polyurethane solution starts to dissolve (and therefore degrade or distort) the polyurethane of the support.

In order to prevent unwanted interaction between the support and the solvent, the support is first coated with a protective barrier layer. In the preferred embodiment, this protective barrier layer is a layer of gold/palladium.

The gold/palladium layer is applied to the support using a DC sputterer, such as a sputterer for use in applying thin gold coatings to samples for observation in a scanning electron microscope (SEM). The inventor has found that suitable deposition conditions, for a target to specimen distance of about 50 mm are about 2.5 kV and a suitable pressure of argon to give a sputter current of about 20 mA.

The thickness of the gold/palladium layer is typically about 35 nm, but coatings of about 300 nm will be effective for certain support architectures, e.g. rougher surfaces.

The inventor has found that the protective barrier layer serves to prevent detrimental attack of the material of the support from the solvent used in the polyurethane solution.

Applying a protective barrier layer to the flexible layer of polyurethane shown in Fig. 4 allows the formation of a further layer over the top of that first layer (here, the first layer of polyurethane is the "support"). In this way, multiple layers of polyurethane can be built up into a laminate, to give rise to laminated valve leaflets that are relatively thick, and therefore relatively crack or tear resistant. Each layer of polyurethane may have an average thickness of 20-30 μm. The total average thickness of each laminated valve leaflet may be about 100-250 μm, composed of five or more layers of polyurethane, separated by protective barrier layers. Note that the thickness of the valve leaflets is usually non-uniform - the leaflet is typically thicker towards its base (up to 400-500 μm) than at its top edge.

The inventor has found that the incorporation of fibres of relatively high Young's modulus into a polymer matrix formed of relatively low Young's modulus material can give rise to beneficial effects for a synthetic prosthetic heart valve.

In one embodiment, the polyurethane solution described above is supplemented with 3 wt% vapour grown carbon fibres. Suitable vapour grown carbon fibres are known and have diameters in the range 0.1-10 μm (typically 70-200 nm diameter). The lengths of the fibres may be up to 1 mm or more (typically in the range 50-100 μm). The Young's modulus of the fibres is between 100 GPa and 300 GPa. The tensile strength of the fibres is around 4 GPa.

The effect of incorporating the carbon fibres into the polyurethane layer is to reinforce the polyurethane layer against cracking or tearing, i.e. the fibres tend to increase the toughness and/or strength of the layer.

An example of the effect of the reinforcing fibres is shown in Figs. 5 to 8. Fig. 5 shows a light micrograph of part of a polyurethane layer produced as set out above from polyurethane solution without any reinforcing fibres. The photograph is a transmission light micrograph, so the sample is shown as being relatively transparent. The polyurethane layer has a cut formed in its side edge using a razor blade. Fig. 6 shows the same sample (a larger portion of the same area of the same sample) after 1000 cycles of a particular load applied by a bench-top tensometer. As seen in Fig. 6, a tear has

extended from the crack into the sample due to the cyclical loading.

Fig. 7 shows a light micrograph of part of a polyurethane layer produced as set out above from polyurethane solution with 3 wt% vapour grown carbon fibres. The image is also a transmission light micrograph, but the incorporation of carbon fibres into the polyurethane makes the sample substantially opaque, so the image is darker than that shown in Figs. 5 and 6. The magnification of the image of Figs. 5-8 is the same. As seen in Fig. 7, a cut is made near the left hand edge of the sample using a razor blade. The cut is of similar length to the cut made in Fig. 5. Fig. 8 shows the same sample (a larger portion of the same region of the same sample) after substantially identical mechanical testing to that applied to the sample shown in Fig. 6. As is clear from the image shown in Fig. 8, the cut has not progressed into a deep tear. Accordingly, the inclusion of reinforcing carbon fibres into the polyurethane layer improves the resistance of the layer to tearing or cracking under cyclical loading.

In an alternative embodiment, carbon nanotubes can be used to reinforce the polyurethane layer. Carbon nanotubes themselves are known. Currently-available carbon nanotubes are relatively short. They can be

single walled (SWNT) or multi-walled (MWNT). A carbon nanotube tube can have an extremely high Young's modulus (e.g. 600 GPa to 1.3 TPa). Bundles of nanotubes may have a lower Young's modulus (e.g. about 100 GPa).

The present inventor uses MWNT having a mean diameter of 10 nm with an average length of around 50 μm. The nanotubes are purified to 95% or higher. It is found that the tear and crack propagation resistance of a polyurethane layer incorporating such carbon nanotubes is improved.

In another embodiment, carbon nanotubes are used that are functionalised with NH_2 groups. In still another embodiment, carbon nanotubes that are functionalised with COOH groups are used. This enhances the interface between the polymer and the nanotubes via interaction between the functional groups on the nanotubes and the NH_2 and/or OH groups or other groups present in the polymer.

In a preferred embodiment, the polyurethane solution described above is prepared by first adding the functionalised carbon nanotubes described above, ultrasonically agitating the mixture and then carrying out electrostatic spinning of the liquid into a grounded container. The liquid contains sufficient solvent that the resultant product is still a liquid, with the

polyurethane still in solution. The effect of the electrostatic spinning is to disperse the nanotubes within the liquid, due to the high charge applied during the electrostatic spinning process. The use of functionalised carbon nanotubes allows the nanotubes to bond to the polymer. This means that, as the charge leaks away, the nanotubes are less likely to clump together.

The liquid prepared by electrostatic spinning is used for dip coating onto a mould for the formation of a flexible polymeric layer, as described above. The dispersion of the carbon nanotubes by electrostatic spinning has a residual effect in the solidified flexible polymeric layer. The electrical resistance of the polymeric layer is significantly lower when the carbon nanotubes are dispersed by electrostatic spinning. This is indirect evidence of uniform dispersion of the carbon nanotubes in the polymeric layer.

The inventor has found that the application of a porous layer between the support and the flexible polymer layer can give rise to a useful keying effect between the flexible polymer layer and the support.

A preferred method for applying the porous layer to the support is to electrostatic spin (ESS) a fine mesh of

polymer fibres onto the surface of the support. The method of electrostatic spinning is known. See, for example, US-A-2004/0079374, which discloses a unidirectional flow prosthetic implant with a layer of ESS material formed on a frame.

ESS requires a strong electric field to form an unstable jet of liquid. In this case, the liquid is a solution of polymer in a solvent. The solvent is a solvent that also dissolves the material of the support. In a particularly preferred embodiment, the material of the support is the same or similar to the material being applied to the support by ESS. Specific suitable polymers have already been mentioned. Of most use are polyetherurethane, polyetherurethane urea, polycarbonaturethane, or any of these formulated with a silicone co-soft segment or with surface modifying end groups such as silicone, fluorocarbon, polyethylene oxide, sulphonate, hydrocarbons or mixtures of these. A biostable formulation is preferred. The ESS of these materials tends to give rise to molecular alignment. In turn, this gives rise to increased strength of the material compared to its bulk form. Accordingly, the mechanical properties of the mesh spun onto the support are different to those of the bulk material. For example, the spun fibres may have a Shore hardness of 50-85D. In an alternative embodiment, the material of the spun fibre mesh is

different to that of the support. In that case, it is still preferred that the solvent is one that is capable of dissolving the material of the support.

Fig. 9 shows an SEM micrograph of a spun fibre mesh formed on a glass slide. As can be seen clearly in this image, the fibres are of around 1 μm thickness and are formed with no preferred orientation. There are large open pores in the structure between the fibres, extending through the mesh. This image was taken some time after the spinning of the mesh and so there is some relaxation in the shape of the fibres.

After the fibre mesh is spun onto the support, a protective barrier layer of gold-palladium is applied, as set out above. The effect of this is to protect the mesh from being degraded by solvent applied in later process steps. The efficacy of the protective barrier layer has been tested. In the test, two similar layers of polyurethane fibre mesh (PurSpan^{tm}) were spun onto glass slides. The thickness of the layers was about 10mm. One subsequently has a protective barrier layer of gold-palladium applied, as described above. Both samples were then dipped into a solvent (dimethylacetamide) for 5 minutes and allowed to dry in air. This solvent would normally dissolve the material of the mesh. The sample having a mesh without a protective barrier layer was

completely removed from the glass slide. The other sample was unaffected, according to visual inspection.

This test shows that the protective barrier layer is effective in substantially preventing attack of the underlying mesh from solvent.

It is preferred not to apply a protective barrier layer between the support and the fibre mesh. This is because the fibre mesh should preferably be firmly attached to the support. When the support is formed of a material that dissolves in the solvent used for the ESS process, the ESS process delivers a viscous liquid consisting of the material of the fibres plus a small amount of solvent to the surface of the support. Before it is driven off, the small amount of solvent interacts with the surface of the support to form a bond between the material of the fibre and the support. This is one of the ways in which a firm bond between the mesh and the support is provided.

This methodology is applied in the production of a flexible polymeric layer formed on a support. First, as described above, a porous mesh of polymer fibres is spun onto the surface of the support (with no protective barrier layer between the mesh and the support). The mesh is about 5 μm thick. Then, a protective barrier layer of gold-palladium is applied to the mesh. Then, a

layer of flexible polymer is formed over the mesh by dip coating, as described above. The dip coating allows a solution of the polymer material of the flexible polymer layer to flow into the open pores in the mesh. The fibres of the mesh are substantially unaffected by the solvent due to the protective barrier layer. Before drying, the layer of solution has an interface region where the solution has flowed into the open pores of the mesh and an overlying region of excess solution. After drying, the flexible layer of polymer has a corresponding interface region in which the layer is keyed into the mesh. The final (dried) thickness of the dip-coated layer plus the mesh is about 30 μm thick.

It will be understood that the above process can be repeated, the flexible polymer layer being the support for a further layer of fibre mesh, a protective barrier layer being applied to that mesh and a further layer of flexible polymer being formed over the mesh as described above. In this way, a laminate structure can be obtained. It is found that such a structure has advantageous properties of tear and crack resistance on repeated loading compared to a single layer of the flexible polymer alone, of the same thickness.

Fig. 10 shows a transmission optical micrograph of a laminate consisting of a first layer of dip-coated

polyurethane (the support) with a spun fibre mesh of polyurethane fibres formed over that first layer, a protective barrier layer of gold-palladium formed over the mesh and a second layer of dip coated polyurethane formed over the mesh.

Figs. 11-23 show schematic cross sectional views of the progressive build-up of layers of a flexible polymeric structure according to a preferred embodiment of the invention. Note that the relative thicknesses shown in these drawings are schematic only.

In Fig. 11, a support 10 is shown in schematic cross section. In this example, the support is a first layer of polyurethane. It is to be understood that it could equally be a more rigid support, such as a polyurethane frame.

In Fig. 12, a first mesh layer 62 of polymer strands is applied to the surface of the first polymer layer by ESS. As described above, the mesh adheres to the first polymer layer due to the small amount of solvent contained in the strands as they reach the polymer layer.

In Fig. 13, a protective barrier layer of gold-palladium is applied to the first mesh layer 62 to give a protected mesh layer 64.

In Fig. 14, a second layer of polymer 66 is applied by dip coating. This second layer of polymer interpenetrates with the protected mesh layer 64, allowing keying of the second polymer layer 66.

In Fig. 15, a second mesh layer 68 of polymer strands is applied to the surface of the second polymer layer 66 by ESS.

In Fig. 16, a protective barrier layer is applied to the second mesh layer 68 to give second protected mesh layer 70.

In Fig. 17, a third polymer layer 72 is applied by dip coating. This third layer of polymer interpenetrates with the second protected mesh layer 70, allowing keying of the third polymer layer 72.

In Fig. 18, a first carbon nanotube reinforced layer of polymer 74 is applied to the third layer of polymer 72 by dip coating as described above.

In Fig. 19, a third mesh layer 76 of polymer strands is applied to the surface of the first carbon nanotube reinforced layer of polymer 74 by ESS. This is subsequently coated with a protective barrier layer in

Fig. 20 to provide a third protected mesh layer 78. A fourth layer of polymer 80 is applied to the third protected mesh layer 78, as shown in Fig. 21.

Additional layers of carbon nanotube reinforced polymer 82, protected mesh layers 84 and polymer layers 86 are applied as appropriate, as shown schematically in Fig. 22.

When the desired number of layers has been built up, a final surface layer of polymer material 88 is applied. In the case where the material is used as a prosthesis in the body, it is not considered that the outer surface should be a protective barrier layer such as gold or gold-palladium because such a layer is likely to be abraded away in use, particularly where the prosthesis is used in cardiovascular applications in contact with flowing blood.

Figs. 24 to 33 show SEM micrographs of laminated constructs formed according to embodiments of the invention.

Fig. 24 shows a cross-sectional SEM micrograph of a construct formed with a series of alternating layers of polymer, spun fibre mesh and protective barrier layer. As is seen in this image, the construct retains its

laminated structure, even after the many process steps required to form all of the layers.

Fig. 25 shows another cross-sectional SEM micrograph of a construct formed with a series of alternating layers of polymer, spun fibre mesh and protective barrier layer. The arrows indicate the boundaries between layers of spun fibre mesh with the protective barrier layer and the overlaid thin polymer layer.

Figs. 26, 28 and 30 show cross-sectional SEM micrographs of constructs formed with a series of alternating layers of polymer, spun fibre mesh and protective barrier layer. Again the arrows indicate the boundaries between adjacent layers. Figs. 27, 29 and 31 respectively shows the corresponding images taken using X-ray elemental analysis. The bright regions correspond to regions having a high concentration of gold.

Fig. 32 shows a cross-sectional SEM micrograph of a freeze-fracture surface of a polymer layer incorporating vapour-grown carbon fibres as reinforcing fibres. Fig. 33 is an enlarged view of a portion of the image of Fig. 32. In these images, the vapour-grown carbon fibres are seen as white strands.

It will be clear how the method shown in Figs. 1 to 4 can be modified to give a valve with flexible leaflets formed with a laminated structure incorporating ESS meshes, protective barriers layers and carbon fibre reinforced polymer layers.

In the embodiments described above, two or more flexible polymer layers are laminated so as to provide improved crack or tear resistance of the construct. The present inventor has realised that the method of forming the laminates can be modified so as to provide different layers having different residual stresses in different shapes or geometries.

In this modified embodiment, the method shown in Figs. 1 to 4 is modified so that, after the formation and drying of the flexible polymer layer in Fig. 3, the frame and flexible polymer layer is removed from the mould 10 and fitted onto another mould (not shown), having a different shape to that of mould 10. This second mould has an overall cylindrical shape of similar dimensions to mould 10 but without the recesses. Fitting the frame and flexible polymer layer onto this second mould deforms the flexible polymer layer by bending. Using the methods described above, a mesh layer is applied to the flexible polymer layer and a protective barrier layer is applied to the mesh layer. Next, a second flexible polymer layer

is applied over the protected mesh layer, as described above. After drying, the second flexible polymer layer is in its preferred shape - conforming to the shape of the second mould. However, this shape is different to the preferred shape of the first flexible polymer layer, i.e. the shape conforming to the shape of the first mould 10. When the construct is removed from the second mould, the flexible polymer layers urge towards their preferred shapes. Thus, the construct has two preferred shapes. In use as a heart valve, this means that the valve leaflets are bistable - they prefer either to be in the closed configuration (corresponding to the shape of the first mould) or in the open configuration (corresponding to the shape of the second mould). This can provide reduced resistance of the valve leaflets to opening and closing.

In a further development of this embodiment, the valve leaflets may be formed with other preferred shapes by using another mould shape for one or more of the flexible polymer layers. For example, a mould corresponding to a semi-open position of the valve leaflets may be used for the majority of the flexible polymer layers. Further layers can be applied using moulds corresponding to fully open and fully closed, as described above. In this way, the dynamics of the leaflet movement in use can be tuned according to the exact requirements of the application.

Alternatively, a single flexible mould may be used to mould the different shapes, the flexibility of the mould allowing alteration of the shapes of the leaflet-moulding surfaces of the mould.

Figs. 34-39 show schematically an alternative methodology to that of Figs. 1-4 for forming a synthetic flexible leaflet heart valve.

In Fig. 34, a mould or former 100 has a similar general form to mould 10 shown in Fig. 1 except that the leaflet-moulding surfaces 102, 104 of the mould do not meet at a sharp ridge. The leaflet-moulding surfaces 102, 104 are in a more opened position than shown in Fig. 1. Further details about this are set out below. Leaflet-moulding surfaces 102, 104 continue upwards to cap portion 106. A frame 101 is located at the lower end of the mould 100, similarly to the embodiment described with respect to Figs. 1-4.

Fig. 35 shows the mould 100 and frame 101 of Fig. 34 after moulding and drying a polyurethane layer 108 over the mould 100 and the outer surface of the frame 101. As can be clearly seen, polyurethane layer 108 is formed as a continuous layer, including a cap portion layer moulded over the cap portion of the mould. Thus, the

polyurethane layer is substantially airtight as there is no opening (yet) at its upper end. The formation of the polyurethane layer with the cap portion layer facilitates the run-off of the polymer solution from the leaflet portions of the layer, thereby increasing the uniformity of the leaflets.

Subsequently, as shown in Fig. 36, a central plug portion 112 is removed from a correspondingly-shaped through-hole 114 in the mould 100. Then, as shown in Fig. 37, a gentle flow of fluid such as water or air (water is preferred) can be used to detach the polyurethane cap and the remainder of the polyurethane layer from the mould. Note that this flow does not detach the polyurethane layer from the frame. There is a strong adherence between the polyurethane layer and the frame for the reasons set out above in relation to the formation of the flexible polymeric layer on a suitable support such as a frame.

The moulded polyurethane layer and frame can then be removed from the mould, as shown in Fig. 38. An occluding disk 116 is inserted into the open end 118 of the frame 101. Occluding disk 116 has a fluid conduit 120 extending through it. Other than the fluid conduit 120, occluding disk forms a substantially airtight seal with the open end 118 of frame 101.

With the occluding disk located as described with respect to Fig. 38, air (or another suitable fluid) is used to distend the polyurethane layer by inflation. The frame is relatively rigid, so the parts of the polyurethane layer supported on the frame are not distended. However, the parts of the polyurethane layer above the frame are distended. Typically, the inflated shape takes the form of a rounded cone or dome.

It has been found that the distension of the polyurethane layer in this way provides a very suitable substrate for electrostatic spinning. One reason for this is that the smooth nature of the inflated surface allows the polymer mesh produced by electrostatic spinning to be deposited relatively uniformly. It has been found that, if the surface to be deposited on includes ridges and peaks, then the polymer mesh tends to deposit preferentially at those ridges and peaks.

If preferential deposition of the polymer mesh is wanted at ridges and peaks of the valve (this may be desirable for reinforcement, for example) then the same apparatus may be used to deflate (i.e. collapse) the polyurethane layer. This is shown in Fig. 39, the polyurethane layer being collapsed from its natural configuration by suction applied to the fluid conduit 120.

Similar inflation and deflation techniques may be used to form preferred shapes for the polyurethane layer, so that further layers may be deposited over the earlier polyurethane layer(s) with a different preferred shape. If necessary to produce a particular shape, a leaflet mould of that particular shape (a different shape to mould 100) may be inserted into the part-manufactured valve before applying suction. Subsequent application of suction then pulls the polyurethane layer against the leaflet-moulding surfaces of the mould to reliably form a subsequent polyurethane layer in that particular shape.

Figs. 40, 41 and 42 show examples of leaflet configurations viewed from above, formed by applying suction in the way suggested with respect to Fig. 39. In Fig. 42, the leaflets are in the completely closed position. Small clips 122 may be applied to the polyurethane cap, just above the leaflets 102, 104 to maintain the shape when suction is released. Note that these drawings show cross-sectional views through the leaflets, at approximately the plane at which the leaflet free edges will be formed later by trimming.

After forming the sequence of layers as described earlier (e.g. with respect to Figs. 11-23), the polymer cap 106 can be removed from the valve, e.g. along lines 105, 107.

This can be done by mechanical cutting, laser trimming or other suitable techniques. This leaves the three flexible leaflets with free ends - these free ends meet when the valve is in its closed configuration. the particular line along which the flexible polymer structure is cut may be chosen as desired, e.g. to provide a bespoke modification to the leaflet free edge shape. The polymer cap can be retained. Since it is formed in the same process as the leaflets, the polymer cap provides a sample of leaflet material that can be used for the purposes of quality control of the leaflets themselves. For replacement heart valves, this can provide information about the likely reliability or otherwise of the leaflets of the heart valve.

There are now described further details of the frame and mould for forming a synthetic flexible leaflet heart valve.

Fig. 43 shows a mould 200 similar to mould 100 of Fig. 34. However, in Fig. 43, mould 200 is shown separate from frame 201. Frame 201 also includes an annular ring portion 203. The upstanding parts of frame 201 include bevelled faces 210 at the internal free edge of the frame. The purpose of these bevelled faces is to allow a smooth transition between the internal surface of the fame and the internal surface of the valve leaflets,

since the leaflets are moulded to the external surface of the frame. (Note that alternative shapes for the free edge of the frame are described below.)

Mould 200 has a trunk portion 211 for locating the frame. A step 213 joins the trunk portion 211 to the leaflet moulding surfaces 202, 204.

Fig. 44 shows a slight modification of the frame of Fig. 43 in that, on frame 251 of Fig. 44, there are two annular ring portions 253 and 253a. These are provided for location of a sewing cuff (not shown). In other respects, Fig. 44 is similar to Fig. 43 except that the frame is located on the mould. As can be seen from Fig. 44, there is a smooth transition between the leaflet moulding surface and the outer surface of the frame, since the width of the step 213 is similar to the thickness of the frame. One benefit of moulding the polymer layer over the outer surface of the frame is that this maximises the diameter of the potential valve orifice when the valve is in the open configuration, for a particular frame diameter.

With the mould structure and frame structure described with respect to Figs. 43 and 44, it is clear that removal of the moulded polymer layer with the frame from the mould is difficult. One option is to cut the cap portion

of the polymer layer and draw the frame and flexible leaflets downwards in Fig. 44. However, if it is preferred to keep the polymer layer in one piece (e.g. if inflation or deflation of the polymer layer is wanted) then it is possible to use a multi-part mould, as illustrated in exploded view in Fig. 45. In this drawing, similar features to those shown in Figs. 43 and 44 are given the same reference numbers. Trunk 211 of the mould is formed integrally with the polymer cap moulding surface. However, the leaflet moulding surfaces 202, 204 (the third leaflet moulding surface is not shown) are formed on separable leaflet moulding portions 260, 262, 264. These attach to the trunk 211 via pegs 266 cooperating with holes 268 in the trunk. With this arrangement, it is possible for the combination of the frame 251, the polymer layer 208 and the leaflet moulding portions 260, 262 and 264 to be removed from the trunk 211. Thus, there is no need to cut the polymer cap from the leaflets in order to remove the mould.

In preferred embodiments, the frame has a wall thickness of about 0.8 mm. This provides an adequate combination of rigidity and flexibility to the frame. Before the frame is fitted to the mould trunk, it may be pre-coated with a polymer layer. For this reason, the internal dimensions of the frame are usually about 0.2 mm larger than the diameter of the trunk. This allows room for the

pre-coat of polymer whilst providing a relatively close fit between the trunk and the frame.

In Figs. 44 and 45, ring portions 253 and 253a are designed to hold a sewing cuff. The sewing cuff is the part that the surgeon sews to attach the replacement valve in position in the patient. In an alternative embodiment to that shown in Figs. 44 and 45, the frame is formed separately from a sewing cuff support portion. This is illustrated in Fig. 46.

In Fig. 46, a frame 301 is provided and has a similar structure to that shown in Fig. 44 except that there are no ring portions for the sewing cuff. Furthermore, the bevelled faces 310 of the frame are provided at the external surface of the frame free edge. A separate sewing cuff support portion 320 is shaped to fit in a suitable position in the patient. It has two ring portions 322 and 324 with a recess between them for retaining a sewing cuff (not shown). Ring portion 322 has a greater radial extent than ring portion 324, to facilitate sewing of the cuff. In use, sewing cuff support portion 320 is attached to the sewing cuff which is then sewn into position in the patient.

After the sewing cuff and the sewing cuff support portion are sewn into position in the patient, the frame 301 can

be attached to the sewing cuff support portion 320. In this example, protrusions 326 fit into recesses 328 to lock the frame to the sewing cuff support portion. However, the locking mechanism may be one of a number of designs such as a bayonet fitting, a screw fitting, an interference clip, magnetic fittings, combinations of these or any other suitable system that ensures that the valve will remain securely in place during the course of its lifetime. The advantage of this embodiment is that the valve is not present whilst the surgeon is sewing, so there is a significantly reduced risk of damage to the valve and the valve leaflets. Another advantage is that the valve can be removed more easily if required (e.g. if a further valve replacement is necessary). A new valve can then be fitted with minimal surgical time to the benefit of both patient and surgeon.

A further embodiment of the frame structure is now described, with reference to Figs. 47 and 48. In these drawings, similar features are given the same reference numerals. Frame 401 is of generally similar structure to frame 251 of Figs. 44 and 45. Ring portions 453 and 453a are provided, but it is to be understood that these could be provided on a corresponding sewing cuff support portion (not illustrated) with suitable locking features on frame 401.

An important feature of frame 401 is the shape of the free edge 410. In use, the valve leaflets are bonded to the frame at the outer surface 412 of the frame. In the closed configuration, the valve leaflets therefore must bend around the free edge of the frame just downstream of the bond of the leaflet to the frame. The sharper the bending of the leaflets, the more likely they are to fail by cracking or tearing. Accordingly, the smooth curving of the outer part 414 of the free edge of the frame provides a support to the bending of the leaflet, reducing the risk of failure of the leaflet at this region. This shape is best shown in the cross-section view of Fig. 48.

A further feature of frame 401 is an overhanging lip 416 formed as an extension of the curved free edge of the frame. This lip projects inwardly into the flow path through the valve. This provides an extended smooth surface for the leaflet to bear against as it flexes from the open configuration to the closed configuration.

A still further feature of frame 401 is the smoothly curved internal edge 418 of the frame at the upstream axial end of the frame. This minimises flow disturbance through the valve.

In manufacturing a synthetic flexible replacement heart valve, it is preferred to produce a valve that provides minimal obstruction to forward flow, minimal backflow, structural durability and low embolic risk. Preferred embodiments of the present invention provide a valve shape that has, in its natural configuration, a shape that is intermediate the open and closed configurations.

The valve shape of the embodiment now described is a development of the valve shape described in detail in Mackay T.G. et al ("New polyurethane heart valve prosthesis: design, manufacture and evaluation", Biomaterials 1996; 17, pp. 1857-1863). The content of that document is hereby incorporated by reference. It is to be understood that the starting point for the present embodiment is the shape of the closed leaflet defined by the relevant elliptical and hyperbolic equations set out in that document.

In the present embodiment, a partially open leaflet geometry is selected for the natural configuration of the valve. This allows the leaflets to open more easily, i.e. the leaflets require lower fluid pressure in order to open.

A mathematical description of the valve or leaflet shape is then used to construct a numerical model of the

leaflet using known 3D CAD software. This model is then exported to mesh generating software. A finite element mesh is generated for each valve leaflet, using 4 node quadrilateral elements, in a format that records vertices, coordinates and the connectivity matrix. This procedure is repeated for each required leaflet. A Fortran code is applied to read the mesh files an generate an immersed boundary (IB) fibre representation consistent with the geometry and materials properties of the leaflets.

The IB method is known from Peskin C. ("The immersed boundary method", Acta Numerica, 2002, 11, pp. 1-39) and Peskin C.S. and McQueen D.M. ("A three dimensional computational method for blood flow in the heart 1. Immersed elastic fibres in a viscous incompressible fluid", Journal of Computational Physics, 1989, 81, pp. 372-405).

Computational modelling is then used to open the closed three leaflet design, represented by the IB code, under conditions simulating pulsatile physiological flow. The desired partially open configurations are chosen according to the time elapsed during the opening cycle of the valve, such as one of the five time "snapshots" illustrated in Fig. 49. In each of the views shown in Figs. 49A-E, the arrow F shows the flow direction. In

Fig. 49A, the valve frame is marked 500 and one of the leaflets is marked 502. Fig. 49A shows the leaflet shape at a time of 0.012 seconds after the beginning of the opening cycle. Fig. 49B shows the leaflet shape at a time of 0.024 seconds after the beginning of the opening cycle. Fig. 49C shows the leaflet shape at a time of 0.028 seconds after the beginning of the opening cycle. Fig. 49D shows the leaflet shape at a time of 0.032 seconds after the beginning of the opening cycle. Fig. 49E shows the leaflet shape at a time of 0.040 seconds after the beginning of the opening cycle.

Once a suitable open configuration is selected, the data for that configuration is imported back into the 3D CAD software package. The CAD software is then used to smooth out wrinkles in the surface of the leaflets to refine the shape to create a partially open design of the desired shape. This design may then be transferred to a CNC milling machine for manufacture of a suitable mould shape. Fig. 50 illustrates the process. A closed valve design 600 is manipulated using the IB method code to partially open the leaflets to give a raw partially open design. This raw model is then refined and smoothed using 3D CAD software to provide the final design 604.

Fig. 51 illustrates an alternative design 606 for the valve. This shape is derived from a later time interval

than shown in Fig. 49. The design is more open than design 604 of Fig. 50.

In the partially-open valve shape, the upstream parts of the leaflets are more open than the leaflet free edges. In particular, bulge portions are formed in the leaflets, adjacent the frame posts. These are the sub-commissural areas of the valve and the advantage of these being partially open is that early opening of the commissural regions of the valve is achieved, ensuring good washout of these regions with blood. Experience has shown that these regions are vulnerable to delayed or reduced opening, making this region at risk of poor washout, reduced blood flow and deposition of platelet or thrombotic material from the blood.

Note that it is possible to replace the computer modelling steps described above with the physical process of manufacturing a closed leaflet and examining its shape during a pulsatile flow using high speed photography.

The synthetic valve formed in accordance with the above description allows a haemodynamic performance comparable to that of mechanical valves, with a thrombo-embolic risk lower than that of mechanical valves, and with durability comparable to, or exceeding, that of biological valves. Of course, many of the techniques described above are

also applicable to other cardiovascular implant devices and/or to other devices for implant with or use with the human or animal body, as will be well understood by the skilled person.

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CLAIMS:

1. A method of manufacturing a flexible polymeric structure for a device for implantation into the human or animal body, the method including the steps:

(i) providing a support of polymeric material;

(ii) applying a protective barrier layer over the support;

(iii) applying a liquid layer including a solvent over the protective barrier layer; and

(iv) removing the solvent from the liquid layer to leave a layer of polymeric material over the protective barrier layer,

thereby sandwiching the protective barrier layer between the support and the layer of polymeric material.

2. A method according to claim 1 wherein the support is another, first, layer of polymeric material.

3. A method according to claim 1 wherein the support is a rigid support member on which the flexible layer of polymeric material is mounted.

4. A method according to any one of claims 1 to 3 including the additional steps of:

(v) applying a further protective barrier layer over the layer of polymeric material;

(vi) applying a liquid layer including a solvent over said further protective barrier layer; and

(vii) removing the solvent from the liquid layer to leave a further layer of polymeric material over said further protective barrier layer.

5. A method according to claim 4 including further sequential steps of applying protective barrier layers and further layers of polymeric material in order to provide a layered flexible polymeric structure having a desired thickness.

6. A method according to any one of claims 1 to 5 including the step of applying an outer layer of polymeric material over the final protective barrier layer.

7. A method according to any one of claims 1 to 6 wherein the protective barrier layer is formed by thin film deposition.

8. A method according to any one of claims 1 to 7 wherein the protective barrier layer is metallic.

9. A method according to any one of claims 1 to 8 wherein the protective barrier layer is formed of a material selected from gold, platinum, silver, palladium,

nickel, copper, chromium or an alloy including at least one of these metals, or carbon.

10. A method according to any one of claims 1 to 9 wherein the liquid used to form the polymeric layer is a solution of the polymer in the solvent.

11. A method according to any one of claims 1 to 10 wherein the polymeric layer is formed by dip-coating.

12. A method according to any one of claims 1 to 11 wherein the polymeric material used for the polymeric layer is of substantially the same composition as that used for the support.

13. A method according to any one of claims 1 to 12 wherein the polymeric material used for each polymeric layer is of substantially the same composition.

14. A method according to any one of claims 1 to 13 including the further step of fixing the flexible layered structure to a frame.

15. A method according to claim 14 including the further step of applying a protective barrier layer over the frame.

16. A layered flexible polymeric structure having a support of polymeric material, a layer of polymeric material and a protective barrier layer sandwiched between the support and the layer of polymeric material.

17. A structure according to claim 16 obtained by the method of any one of claims 1 to 15.

18. An implantable device incorporating a layered flexible polymeric structure according to claim 16 or claim 17.

19. A device according to claim 18 having a frame for supporting the layered flexible polymeric structure.

20. A device according to claim 18 or claim 19 that is a cardiovascular prosthesis for implantation into the human or animal body.

21. A flexible polymeric structure for a device for implantation into the human or animal body, the structure having a polymeric matrix component formed of a polymeric material with a Young's modulus of at most 100 MPa and having disposed within it an arrangement of fibres formed of a material with a Young's modulus of at least 500 MPa in the elongate direction of the fibres, said arrangement of fibres providing the structure with increased

resistance to crack or tear propagation on repeated flexing of the structure in comparison to the material of the matrix component alone.

22. A structure according to claim 21 wherein the matrix material has a Young's modulus of at most 30 MPa to allow the material to be resiliently deformed easily.

23. A structure according to claim 21 or claim 22 wherein the Shore A hardness of the matrix material is at most 95.

24. A structure according to any one of claims 21 to 23 wherein the matrix material comprises a polyurethane elastomer.

25. A structure according to claim 24 wherein the polyurethane elastomeric composition comprises a polysiloxane macrodiol and a polyether macrodiol and/or a copoly(ether carbonate) macrodiol.

26. A structure according to claim 24 wherein the polyurethane elastomeric composition comprises a chain extender including a silicon-containing diol and, optionally, a soft segment macrodiol derived from a polysiloxane macrodiol and a polyether macrodiol.

27. A structure according to claim 24 wherein the matrix material is a siloxane-containing polyurethane-urea elastomeric composition derived from a silicon-containing diamine.

28. A structure according to claim 27 wherein the composition includes a soft segment macrodiol derived from a hydroxy terminated polysiloxane macrodiol.

29. A structure according to any one of claims 21 to 28 wherein the fibre material is carbon fibre.

30. A structure according to any one of claims 21 to 29 wherein the average width of the fibres is less than 5×10^{-6} m.

31. A structure according to claim 29 or claim 30 wherein the fibres are nanotubes with an average width of less than 5×10^{-9} m.

32. A flexible polymeric structure according to any one of claims 21 to 31, formed as a layered structure with a support of polymeric material, with a protective barrier layer sandwiched between the support and the layer of polymeric material.

33. A method of manufacture of a flexible polymeric structure according to any one of claims 21 to 32, the method including the steps of:

forming a layer from a liquid containing the polymeric matrix component, or a precursor thereof, and the fibres; and

removing the liquid.

34. A method according to claim 33 wherein the liquid is a mixture of the fibres and the polymeric matrix component, or a precursor thereof, the liquid being prepared by electrostatic spinning, a charge applied to the liquid during electrostatic spinning serving to disperse the fibres within the liquid, the layer being formed from the resultant liquid.

35. A method according to claim 33 or claim 34 wherein the fibres chemically interact with the polymeric matrix component, or precursor thereof.

36. A method according to claim 35 wherein the fibres are carbon nanotubes that have been functionalised with at least one additional chemical species, for interaction with the polymeric matrix component, or precursor thereof.

37. A method according to any one of claims 33 to 36 wherein, prior to the electrostatic spinning, the liquid is agitated to disperse the fibres through the liquid.

38. A method according to any one of claims 33 to 37 wherein the layer is formed by coating the liquid onto a mould or support.

39. A device for implantation into the human or animal body having:

a support;

a porous layer on a surface of the support to form a keying interface on the surface;

a protective barrier layer formed over the porous layer; and

a layer of flexible polymeric material applied over the protective barrier layer,

wherein an interface part of the layer of flexible polymeric material is interlocked with the porous layer.

40. A device according to claim 39 wherein the porous layer comprises a mesh of fibres.

41. A device according to claim 39 or claim 40 wherein the interface part of the layer of flexible polymeric material includes elements of flexible polymeric material that are trapped in interstices in the porous layer and

that are integral with the layer of flexible polymeric material.

42. A device according to any one of claims 39 to 41 having a further porous layer bonded to a surface of the layer of flexible polymeric material, said further porous layer having a further protective barrier layer and a further layer of flexible polymeric material applied over said further protective barrier layer so that an interface part of said further layer of flexible polymeric material is interlocked with the further porous layer.

43. A device according to any one of claims 39 to 42 wherein the flexible polymeric structure is a laminate of a plurality of alternate layers of porous layer, protective barrier layer and flexible polymer layer, wherein an interface part of each flexible polymer layer is interlocked with its respective porous layer.

44. A device according to any one of claims 39 to 44 wherein the support is a layer of flexible polymeric material.

45. A device according to any one of claims 39 to 44 wherein the support is a relatively rigid member to which

said layer of flexible polymeric material or laminate is attached.

46. A device according to any one of claims 39 to 45 wherein the porous layer is formed of polymeric material.

47. A device according to claim 46 wherein the composition of the porous layer is substantially the same as that of the support and/or the flexible polymer layer.

48. A device according to any one of claims 39 to 47 wherein there is no protective barrier layer formed between the surface of the support and the porous layer in order to allow a firm bond to form between the support and the porous layer.

49. A device according to any one of claims 39 to 48 wherein the material of the porous layer has different mechanical properties to the support and/or flexible polymer layer.

50. A device according to claim 49 wherein the porous layer is a fibre mesh, and the fibres have higher Young's modulus along the fibre direction than the material of the support and/or flexible polymer layer.

51. A method of manufacture of a device for implantation into the human or animal body, including the steps:

(i) providing a support of polymeric material;

(ii) applying a porous layer on a surface of the support to form a keying interface on the surface;

(iii) applying a protective barrier layer over the porous layer;

(iv) applying a liquid layer including a solvent over the protective barrier layer; and

(v) removing the solvent from the liquid layer to leave a layer of polymeric material over the protective barrier layer,

whereby an interface part of the layer of flexible polymeric material is interlocked with the porous layer.

52. A method according to claim 51 wherein the deposition of the porous layer onto the support includes the formation of the porous layer from a solution of the material of the porous layer in a solvent.

53. A method according to claim 52 wherein the deposition of the porous layer onto the support includes rapid removal of the solvent during transit of the solution so that the material applied to the surface of the support has only a small amount of solvent present.

54. A method according to claim 53 wherein the porous layer is a mesh of fibres and is formed by electrostatic spinning.

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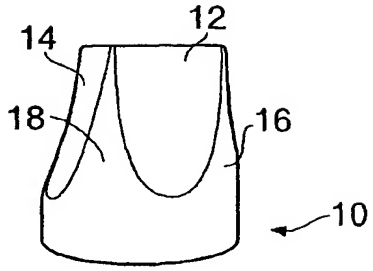

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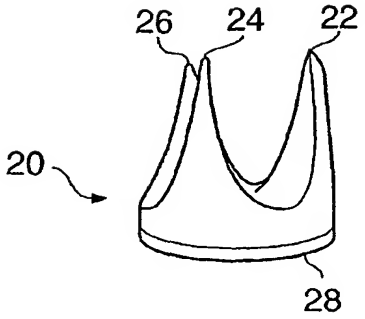


Fig. 2

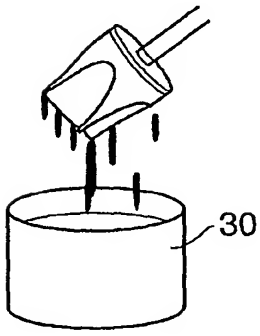


Fig. 3

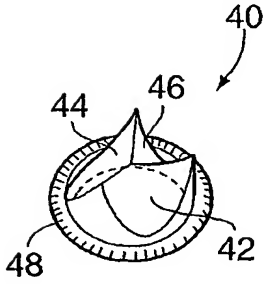


Fig. 4

Fig. 7

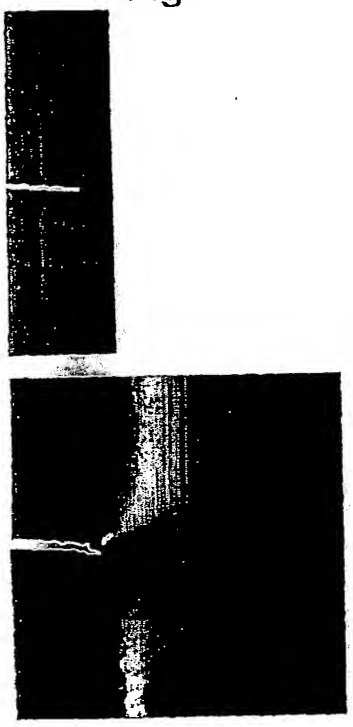
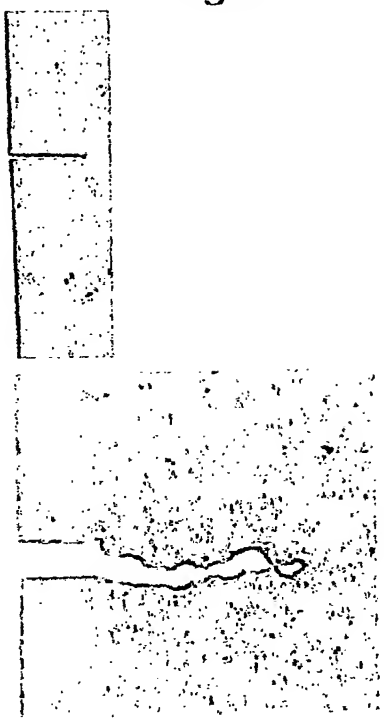


Fig. 8

Fig. 5



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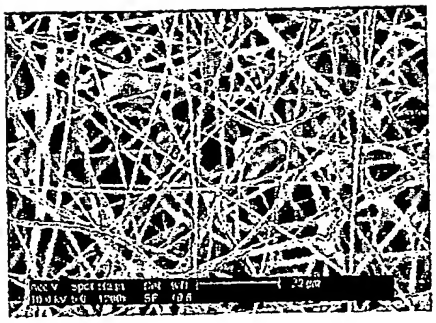

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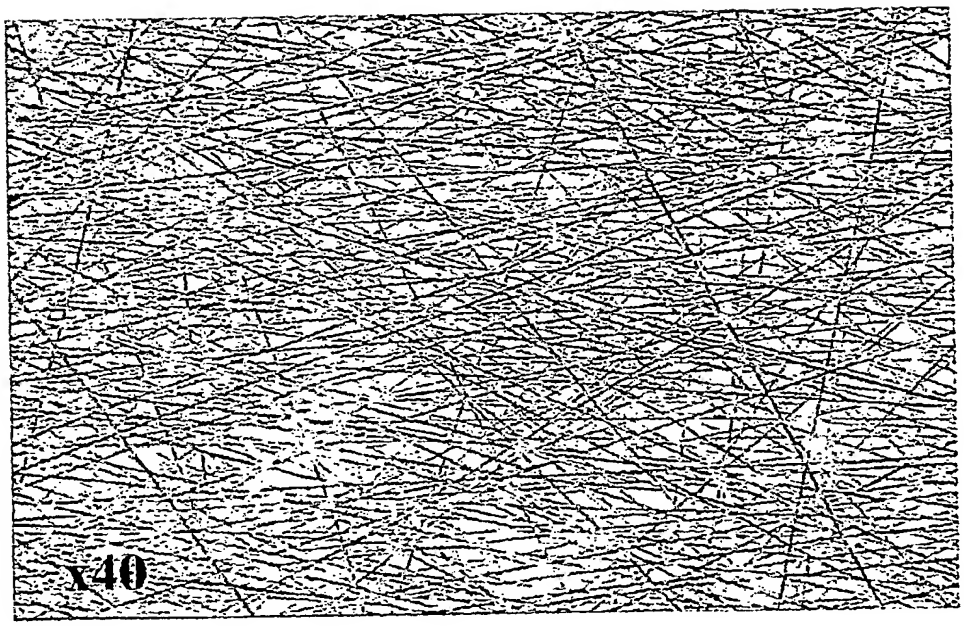
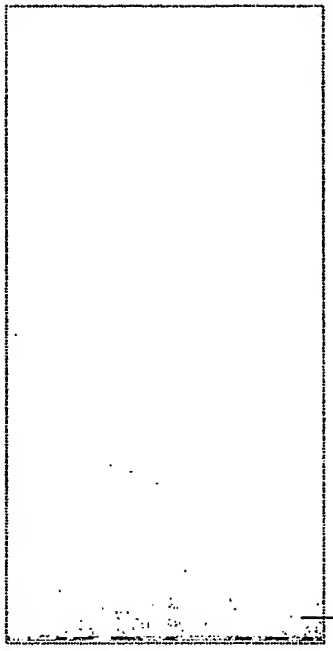


Fig. 10

Fig. 11



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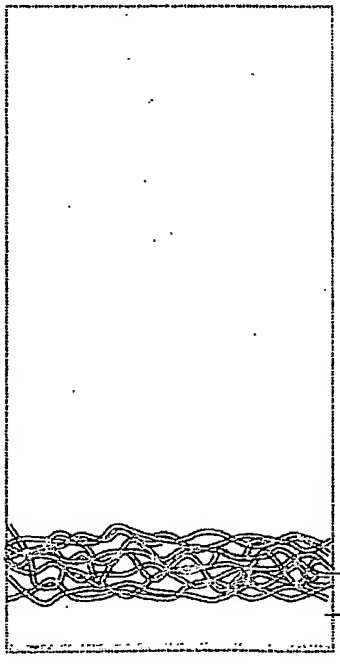

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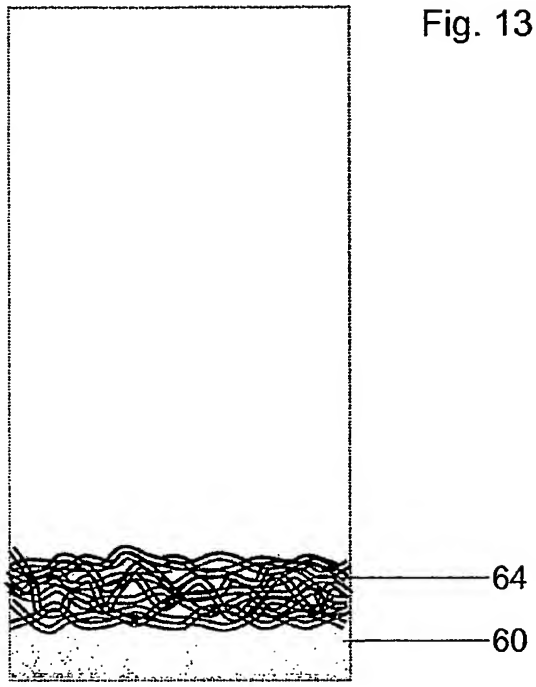

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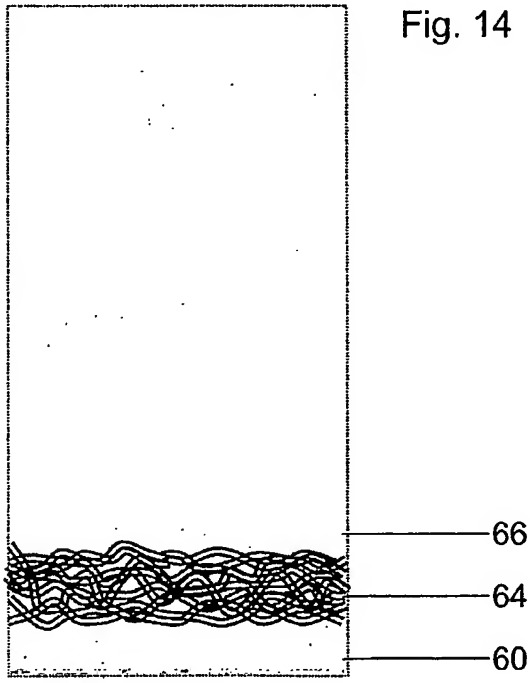

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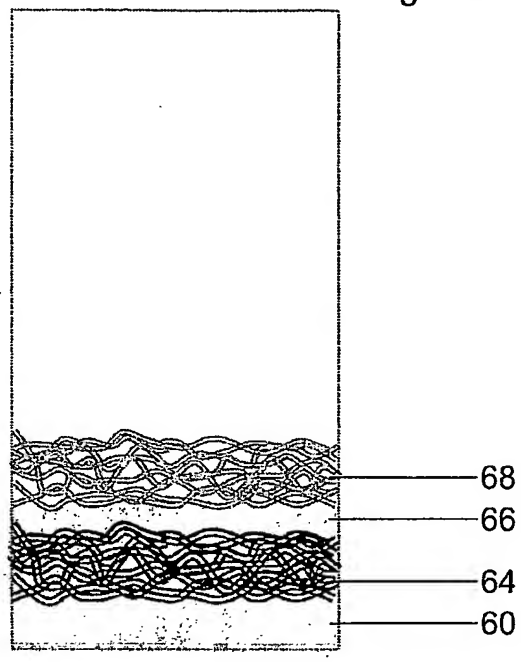

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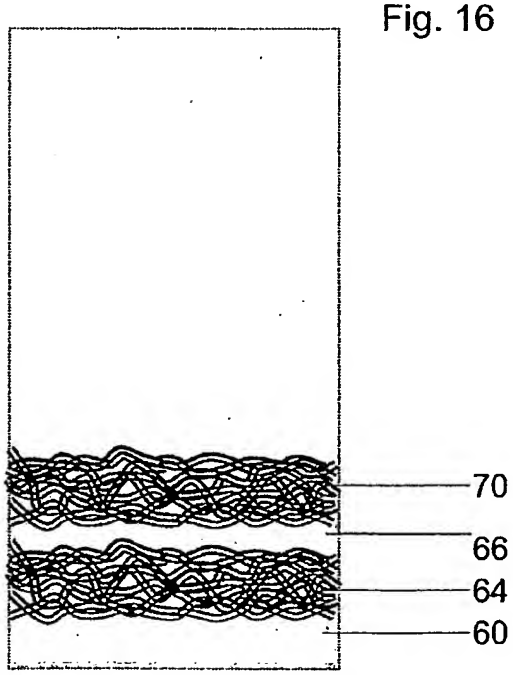

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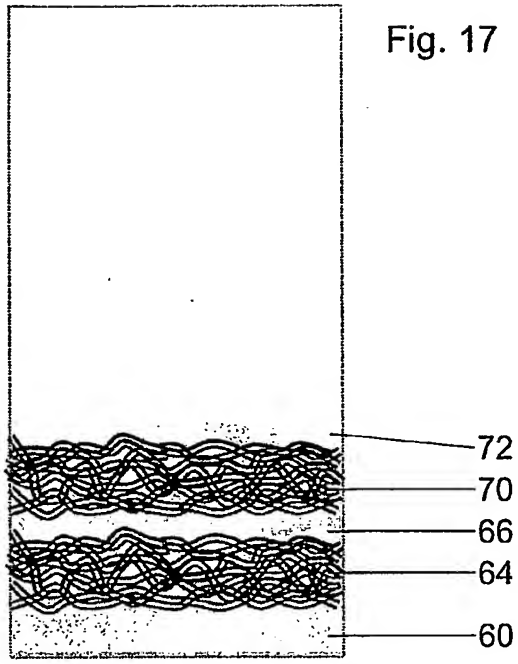

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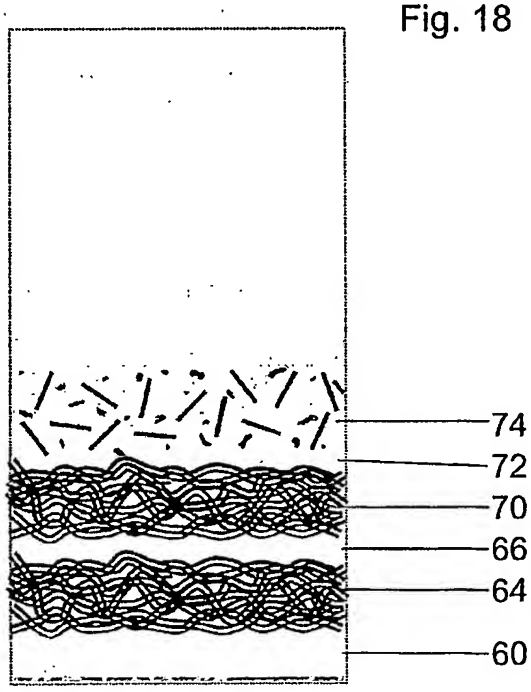

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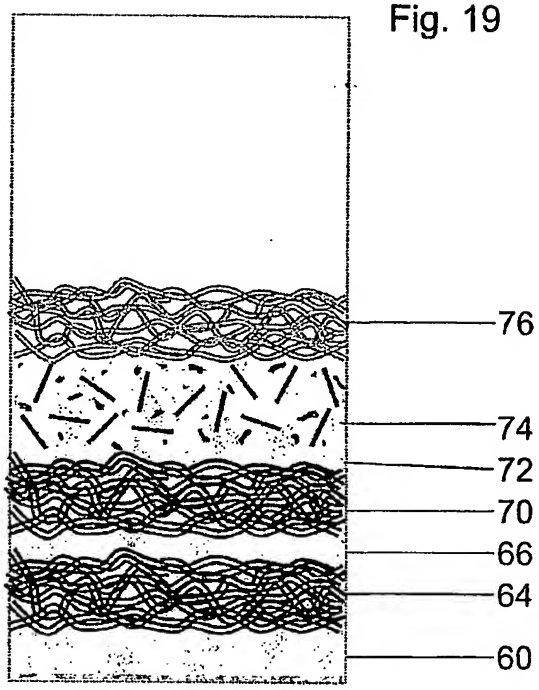

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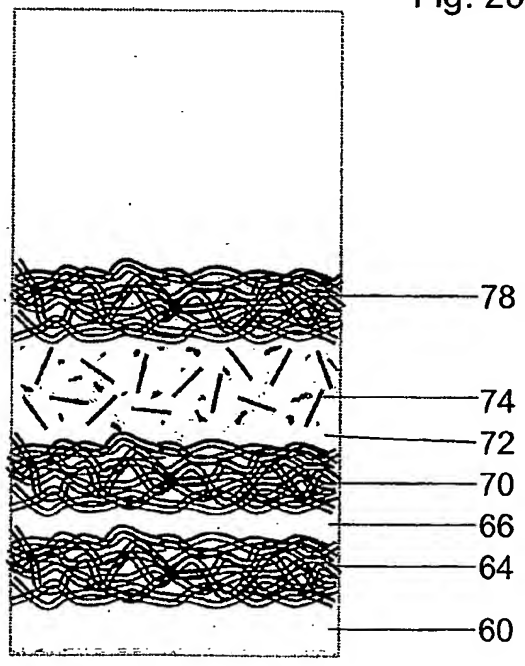

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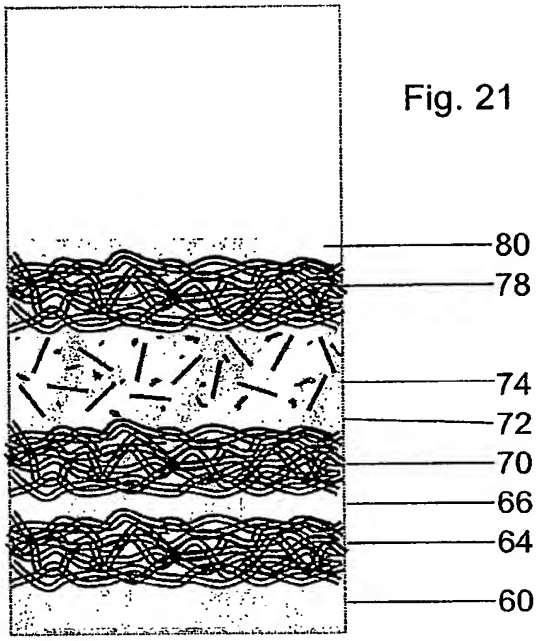

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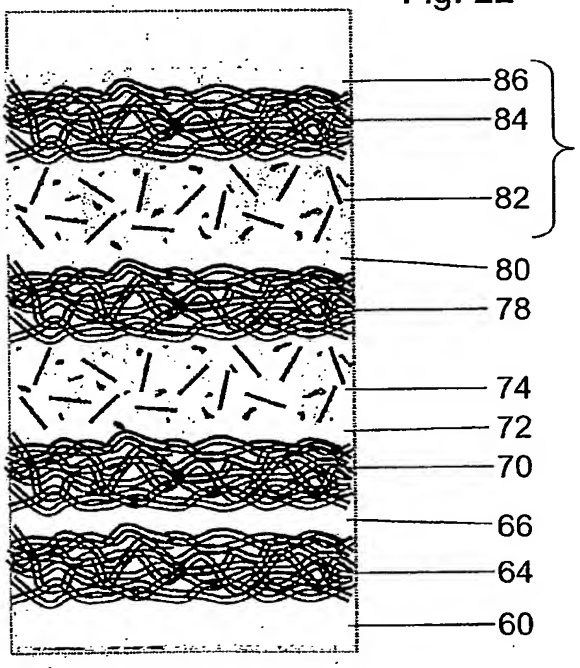

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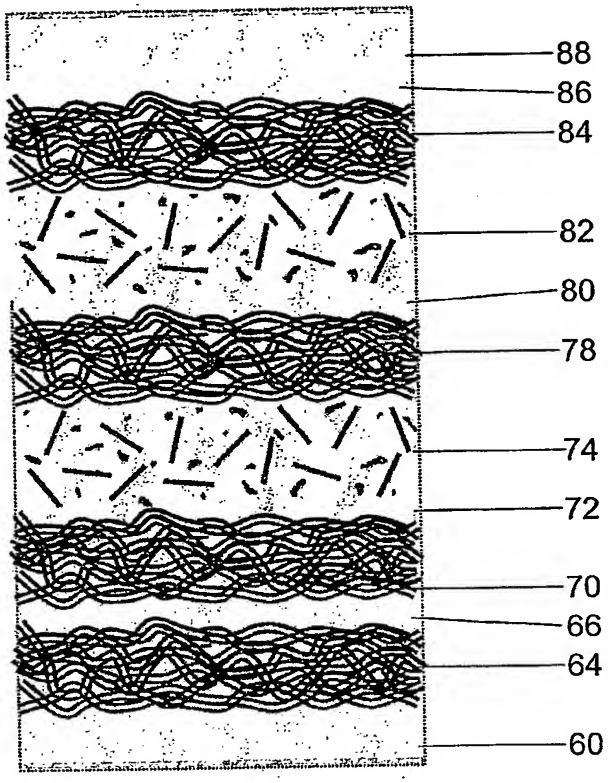

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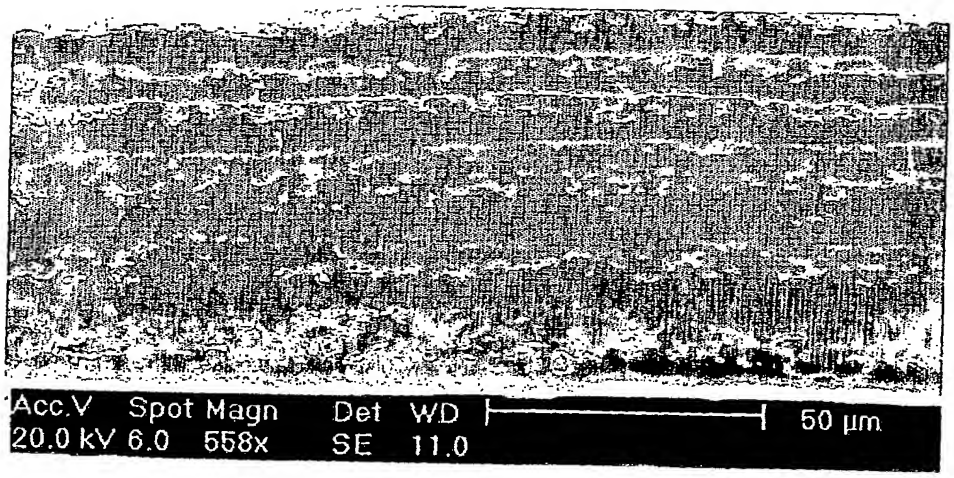
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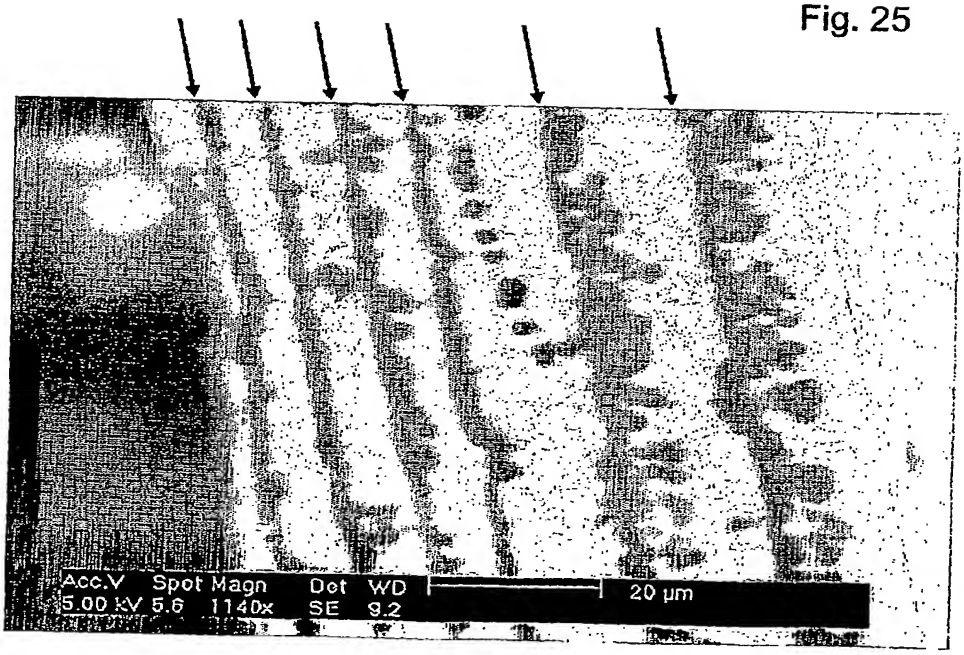
50 µm

Fig. 25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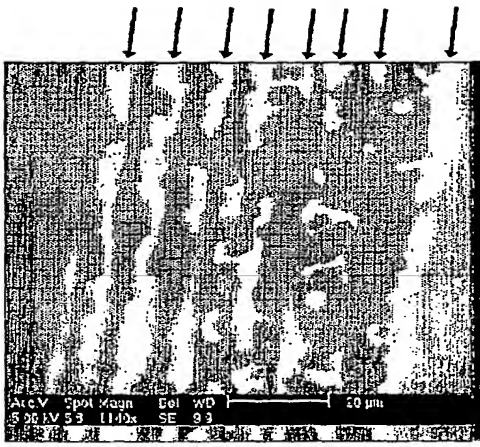
5.00 kV 5.6 1140x SE 9.2
20 µm



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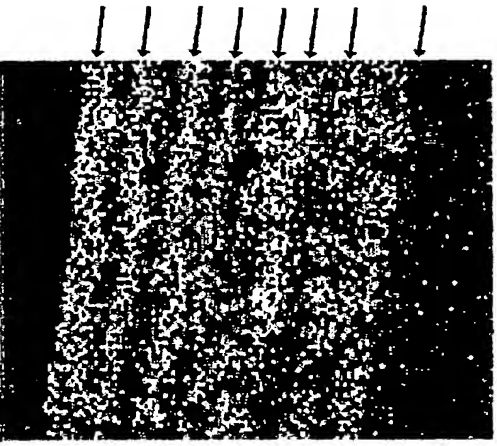

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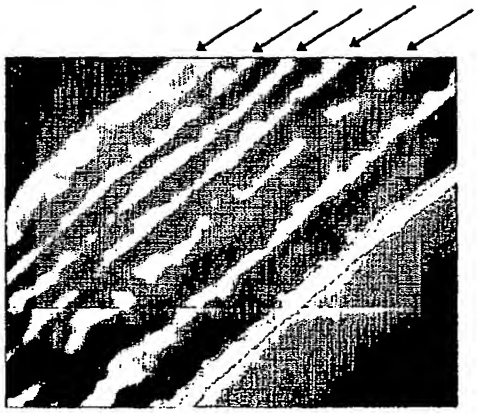


Fig. 28

Fig. 29

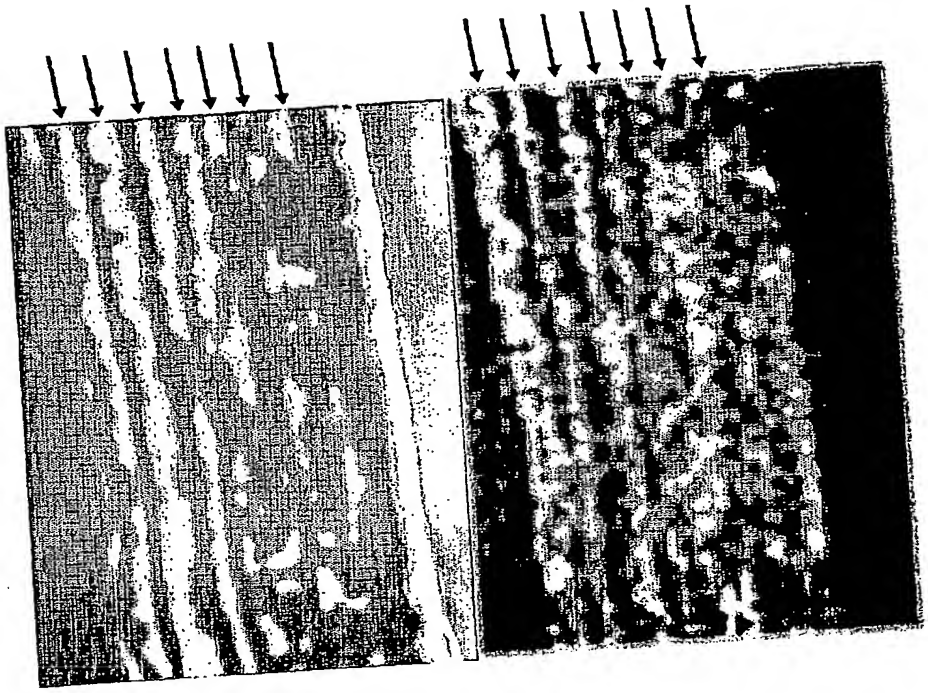


Fig. 30

Fig. 31

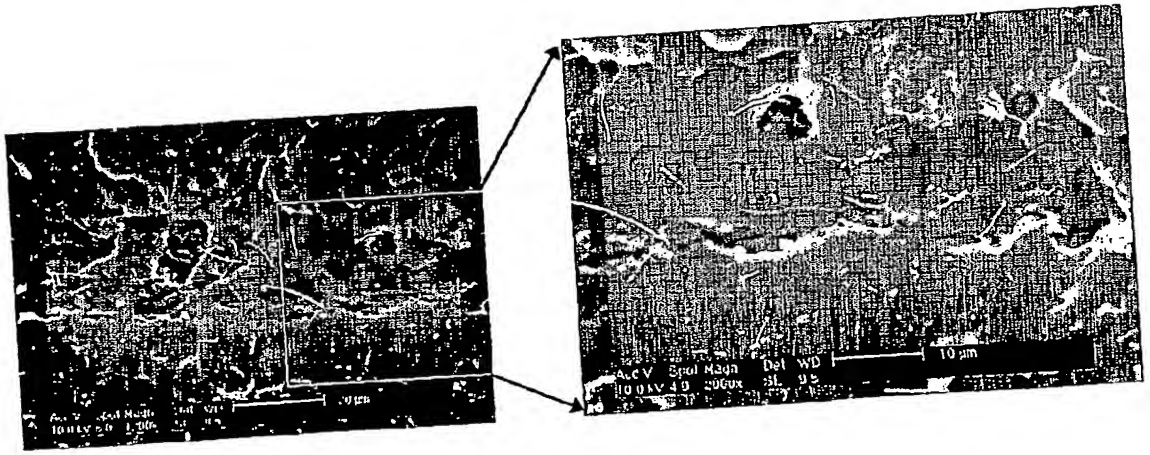
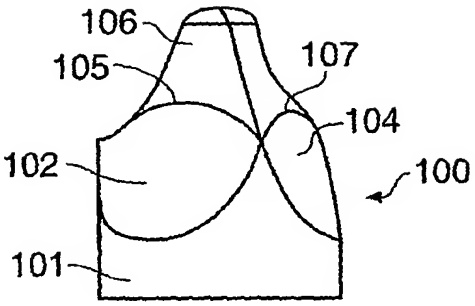


Fig. 32

Fig. 33



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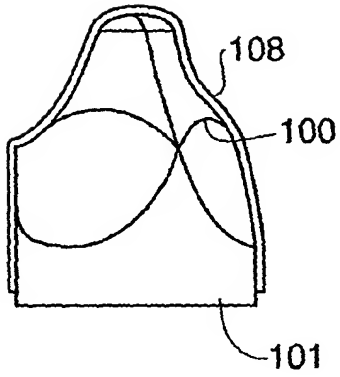

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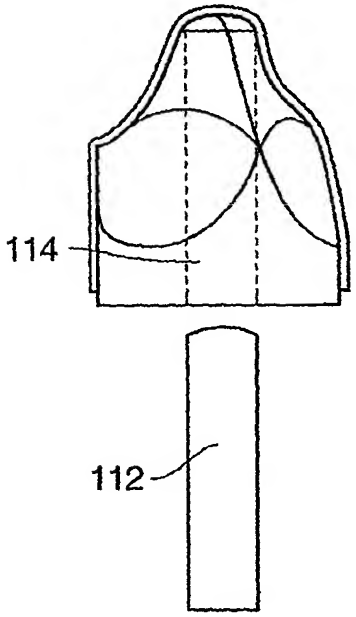

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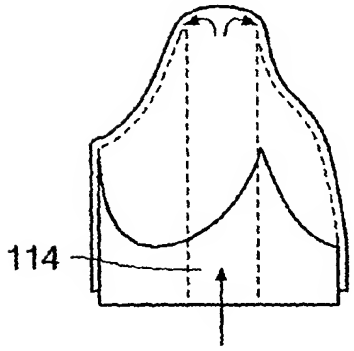

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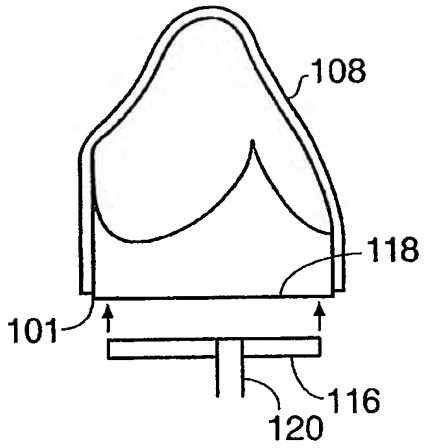

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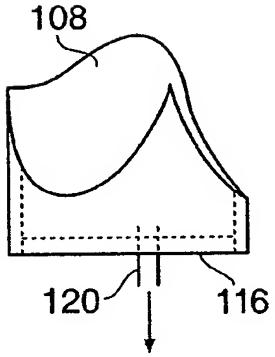

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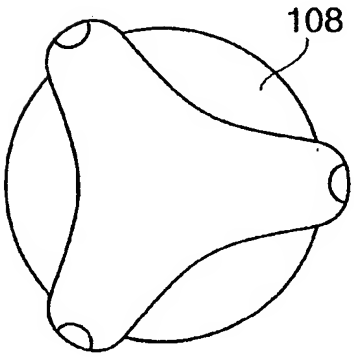

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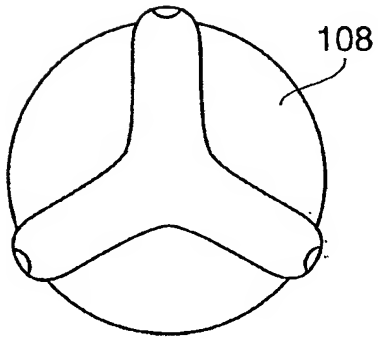

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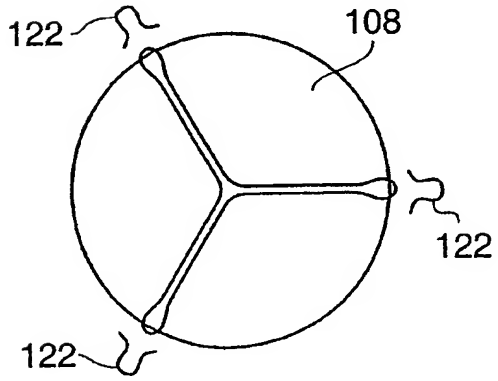

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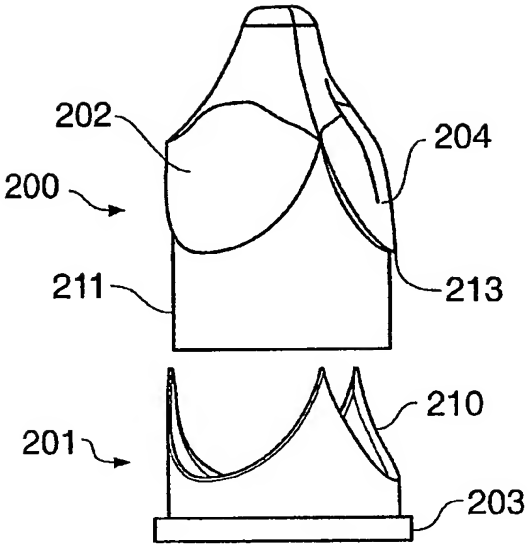

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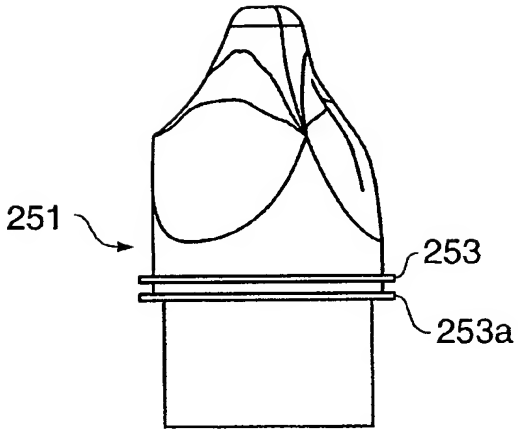

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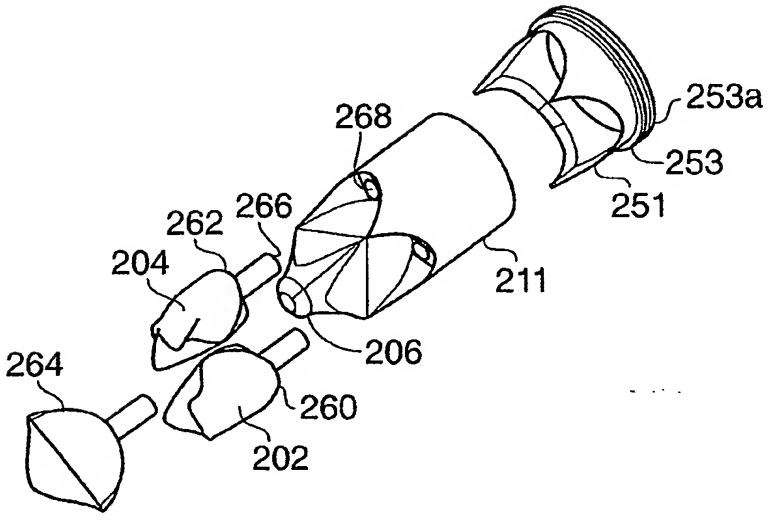

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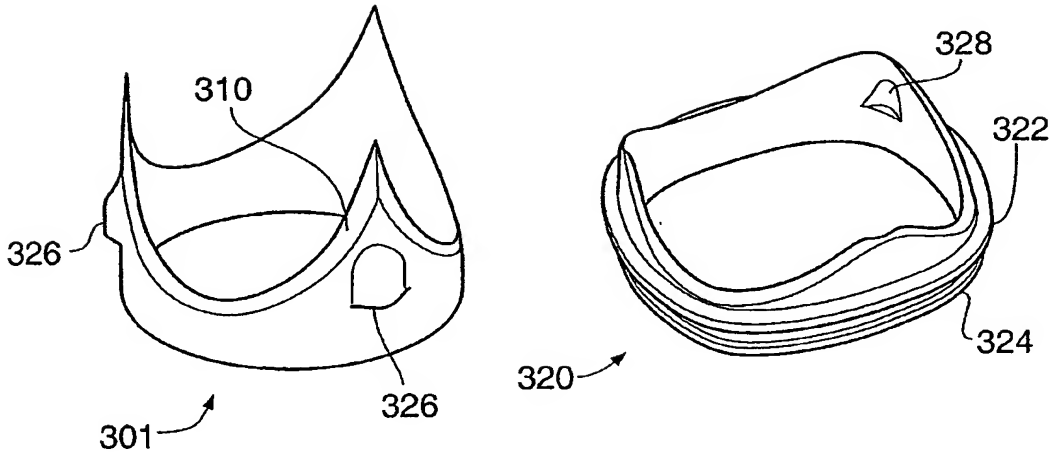

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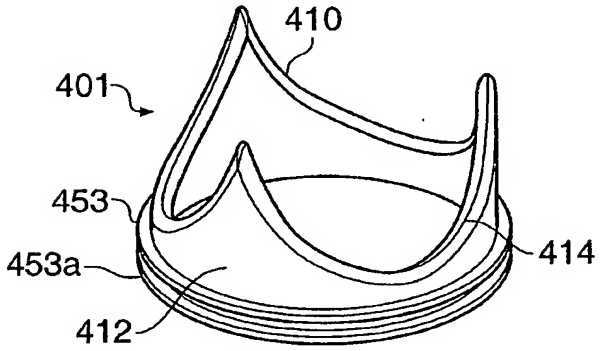

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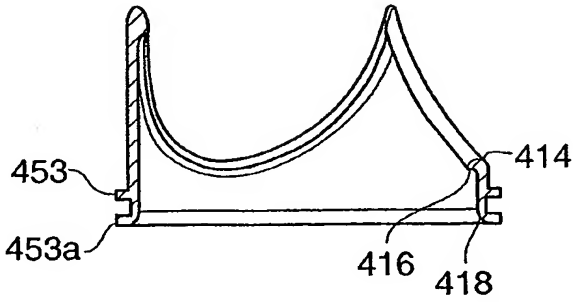

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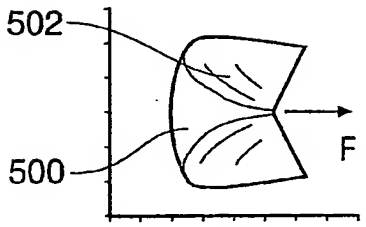
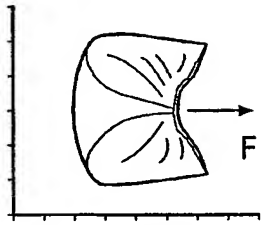


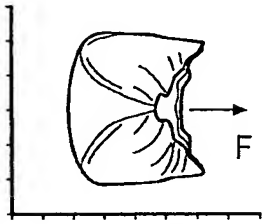
t=0.012s

Fig. 49A



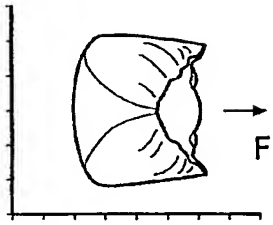
t=0.024s

Fig. 49B



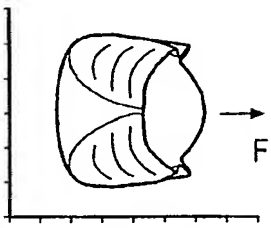
t=0.028s

Fig. 49C



t=0.032s

Fig. 49D



t=0.040s

Fig. 49E

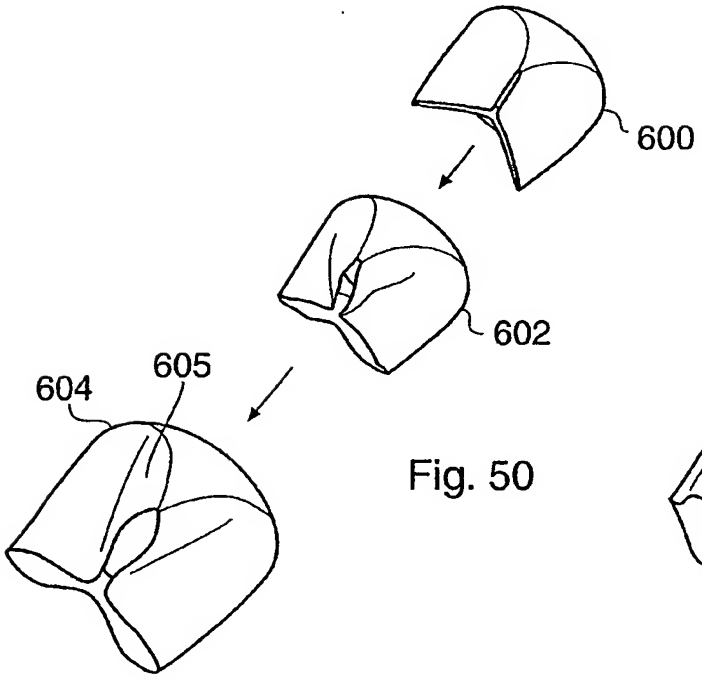


Fig. 50

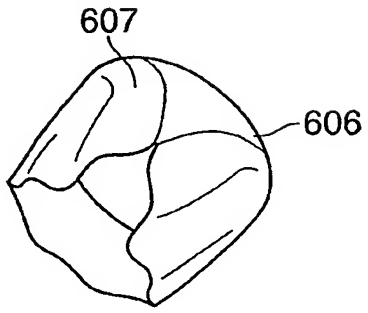


Fig. 51